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**699,183 13 May 1991 (13.05.91) US**(71) Applicant: **MASSACHUSETTS INSTITUTE OF TECHNOLOGY [US/US]; 77 Massachusetts Avenue, Cambridge, MA 02139 (US).**(72) Inventors: **SHARPLESS, K., Barry ; 7902 Roseland Drive, LaJolla, CA 92121 (US). BELLER, Matthias ; Republikstr. 12, D-3501 Eder Munde (DE). BLACKBURN, Brent ; 11 Hillview Court, San Francisco, CA 94124 (US). KAWANAMI, Yasahiro ; 185 Freeman Street, Apt. 735, Brookline, MA 02146 (US). KWONG, Hoi-Lun ; 8 Hammond Street, Somerville, MA 02143 (US). OGINO, Yasukazu ; 175 Freeman Street, Apt. 408, Brookline, MA 02146 (US). SHIBATA, Toinoyuki ; 6-6-1, Higashi-Nippori, Arakawa-ku, Tokyo 116 (JP). UKITA, Tatsuzo ; 25/1403 Takasu-cho 2-1 Nishinomiya-shi, Hyogo 663 (JP). WANG, Lisa ; 348 Beacon Street, Apt. 9, Boston, MA 02116 (US).**(74) Agents: **GRANAHAN, Patricia et al.; Hamilton, Brook, Smith & Reynolds, Two Militia Drive, Lexington, MA 02173 (US).**(81) Designated States: **AT (European patent), BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, LU (European patent), MC (European patent), NL (European patent), SE (European patent).****Published***With international search report.**Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.*(54) Title: **HETEROCYCLIC CHIRAL LIGANDS AND METHOD FOR CATALYTIC ASYMMETRIC DIHYDROXYLATION OF OLEFINS**

## (57) Abstract

Osmium-catalyzed methods of addition to an olefin are discussed. In the method of asymmetric dihydroxylation of the present invention, an olefin, a chiral ligand, an organic solvent, water, an oxidant and an osmium-containing compound are combined. In the method of asymmetric oxyamination of the present invention, an olefin, a chiral ligand, an organic solvent, water, a metallochloramine derivative, an osmium-containing compound and, optionally, a tetraalkyl ammonium compound are combined. In the method of asymmetric diamination of the present invention, an olefin, a chiral ligand, an organic solvent, a metallochloramine derivative, an amine and an osmium-containing compound are combined. In one embodiment, an olefin, a chiral ligand which is a polymeric dihydroquinidine derivative or a dihydroquinine derivative, acetone, water, a base, an oxidant and osmium tetroxide are combined to effect asymmetric dihydroxylation of the olefin.

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HETEROCYCLIC CHIRAL LIGANDS AND METHOD  
FOR CATALYTIC ASYMMETRIC  
DIHYDROXYLATION OF OLEFINS

Background

05        In nature, the organic constituents of animals, microorganisms and plants are made up of chiral molecules, or molecules which exhibit handedness. Enantiomers are stereoisomers or chiral molecules whose configurations (arrangements of constituent atoms) are  
10 nonsuperimposed mirror images of each other; absolute configurations at chiral centers are determined by a set of rules by which a priority is assigned to each substituent and are designated R and S. The physical properties of enantiomers are identical, except for the  
15 direction in which they rotate the plane of polarized light: one enantiomer rotates plane-polarized light to the right and the other enantiomer rotates it to the left. However, the magnitude of the rotation caused by each is the same.

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The chemical properties of enantiomers are also identical, with the exception of their interactions with optically active reagents. Optically active reagents interact with enantiomers at different rates, resulting in reaction rates which may vary greatly and, in some cases, at such different rates that reaction with one enantiomer or isomer does not occur. This is particularly evident in biological systems, in which stereochemical specificity is the rule because enzymes (biological catalysts) and most of the substrates on which they act are optically active.

A mixture which includes equal quantities of both enantiomers is a racemate (or racemic modification). A racemate is optically inactive, as a result of the fact that the rotation of polarized light caused by a molecule of one isomer is equal to and in the opposite direction from the rotation caused by a molecule of its enantiomer. Racemates, not optically active compounds, are the products of most synthetic procedures. Because of the identity of most physical characteristics of enantiomers, they cannot be separated by such commonly used methods as fractional distillation (because they have identical boiling points), fractional crystallization (because they are equally soluble in a solvent, unless it is optically active) and chromatography (because they are held equally tightly on a given adsorbent, unless it is optically active). As a result, resolution of a racemic mixture into enantiomers is not easily accomplished and can be costly and time consuming.

Recently, there has been growing interest in the synthesis of chiral compounds because of the growing demand for complex organic molecules of high optical

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05 purity, such as insect hormones and pheromones, prostaglandins, antitumor compounds, and other drugs. This is a particularly critical consideration, for example, for drugs, because in living systems, it often happens that one enantiomer functions effectively and the other enantiomer has no biological activity and/or interferes with the biological function of the first enantiomer.

10 In nature, the enzyme catalyst involved in a given chemical reaction ensures that the reaction proceeds asymmetrically, producing only the correct enantiomer (i.e., the enantiomer which is biologically or physiologically functional). This is not the case in laboratory synthesis, however, and, despite the interest in  
15 and energy expended in developing methods by which asymmetric production of a desired chiral molecule (e.g., of a selected enantiomer) can be carried out, there has been only limited success.

In addition to resolving the desired molecule from a  
20 racemate of the two enantiomers, it is possible, for example, to produce selected asymmetric molecules by the chiral pool or template method, in which the selected asymmetric molecule is "built" from pre-existing, naturally-occurring asymmetric molecules. Asymmetric  
25 homogeneous hydrogenation and asymmetric epoxidation have also been used to produce chiral molecules. Asymmetric hydrogenation is seen as the first manmade reaction to mimic naturally-occurring asymmetric reactions.

Sharpless, K.B., Chemistry in Britain, January 1986, pp  
30 38-44; Mosher, H.S. and J.D. Morrison, Science,  
221:1013-1019 (1983); Maugh, T.H., Science, 221:351-354

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(1983); Stinson, S., Chemistry and Engineering News,  
\_\_ :24 (6/2/86).

Presently-available methods of asymmetric synthesis are limited in their applicability, however. Efficient  
05 catalytic asymmetric synthesis reactions are very rare; and they usually require a directing group and thus are substrate limited. Because such reactions are rare and chirality can be exceptionally important in drugs, pheromones and other biologically functional  
10 compositions, a catalytic method of asymmetric dihydroxylation would be very valuable. In addition, many naturally-occurring products are dihydroxylated or can be easily derived from a corresponding vicinal diol derivative.

#### 15 Summary of the Invention

Olefins or alkenes with or without proximal heteroatom-containing functional groups, are asymmetrically dihydroxylated, oxyaminated or diaminated using an osmium-catalyzed process which is the subject of  
20 the present invention. Chiral ligands which are novel alkaloid derivatives, particularly dihydroquinidine derivatives or dihydroquinine derivatives or salts thereof, useful in the method of the present invention are also the subject of the present invention.  
20 Derivatives of the parent alkaloids, e.g. quinidine or quinine, or salts thereof can also be used, but the rate of catalysis is slightly slower.

In one embodiment of the present invention, the chiral ligand is immobilized to or incorporated within a  
25 polymer. Both monomeric and polymeric ligands can be immobilized to or incorporated into the polymer. The

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immobilized or incorporated ligands form a complex with the osmium catalyst during the reaction, resulting in efficient catalysis in which the complex can be preserved after the reaction, allowing repetitive use of the  
05 complex. Alternatively, a preformed osmium-ligand complex can be used in the reaction, and recovered.

In the method of asymmetric modification or addition of the present invention, an olefin, a selected chiral ligand, an organic solvent, water, an oxidant, an osmium  
10 source and, optionally, an additive which accelerates hydrolysis of the osmate intermediate are combined, under conditions appropriate for reaction to occur. The method of ligand-accelerated catalysis of the present invention is useful to effect asymmetric dihydroxylation,  
15 asymmetric oxyamination and asymmetric diamination of an olefin of interest. A particular advantage of the catalytic asymmetric method is that only small quantities of osmium catalyst are required.

#### Brief Description of the Drawings

20 Figure 1 is a schematic representation of asymmetric dihydroxylation via ligand-accelerated catalysis which is carried out by the method of the present invention.

Figure 2 is a schematic representation of asymmetric catalytic oxyamination of stilbene which is carried out  
25 by the method of the present invention.

Figure 3 is a plot of amine concentration vs second-order-rate constant  $k$  for the catalytic cis-dihydroxylation of styrene. At point a, no amine has been added. Point a thus represents the rate of the catalytic process  
30 in the absence of added amine ligands. Line b represents the rate of the catalytic process in the presence of

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varying amounts of quinuclidine, a ligand which substantially retards catalysis. Line c represents the rate of the catalytic process in the presence of the dihydroquinidine benzoate derivative 1 represented in Figure 1. K is defined as  $K_{obs}/[OsO_4]_0$  where rate =  $-d[styrene]/dt = K_{obs} [styrene]$ . Conditions: 25°C,  $[OsO_4]_0 = 4 \times 10^{-4} M$ ,  $[NMO]_0 = 0.2M$ ,  $[styrene]_0 = 0.1M$ .

Figure 4 is a schematic representation of a proposed mechanism of catalytic olefin dihydroxylation. This scheme shows two diol-producing cycles believed to be involved in the ligand-accelerated catalysis of the present invention. Formula 1 represents an alkaloid-osmium complex; formula 2 represents a monoglycolate ester; formula 3 represents an osmium(VIII)trioxoglycolate complex; formula 4 represents a bisglycolate osmium ester; and formula 5 represents a dioxobisglycolate.

#### Detailed Description of the Invention

Asymmetric epoxidation has been the subject of much research for more than ten years. Earlier work demonstrated that the titanium-tartrate epoxidation catalyst is actually a complex mixture of epoxidation catalysts in dynamic equilibrium with each other and that the main species present (i.e., the 2:2 structure) is the best catalyst (i.e., about six times more active than titanium isopropoxide bearing no tartrate). This work also showed that this rate advantage is essential to the method's success because it ensures that the catalysis is channeled through a chiral ligand-bearing species.

The reaction of osmium tetroxide ( $OsO_4$ ) with olefins is a highly selective and reliable organic transforma-

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tion. It has long been known that this reaction is accelerated by nucleophilic ligands. Criegee, R. Justus Liebigs Ann. Chem., 522:75 (1936); Criegee, R. et al., Justus Liebigs Ann. Chem., 550:99 (1942); VanRheenen et al., Tetrahedron Lett., 1973 (1976). It has now been shown that a highly effective osmium-catalyzed process can be used to replace previously known methods, such as the stoichiometric asymmetric osmylation method. Hentges, S.G. and K.B. Sharpless, Journal of the American Chemical Society, 102:4263 (1980). The method of the present invention results in asymmetric induction and enhancement of reaction rate by binding of a selected ligand. Through the use of the ligand-accelerated catalytic method of the present invention, asymmetric dihydroxylation, asymmetric diamination or asymmetric oxyamination can be effected.

As a result of this method, two hydroxyl groups are stereospecifically introduced into (imbedded in) a hydrocarbon framework, resulting in cis vicinal dihydroxylation. The new catalytic method of the present invention achieves substantially improved rates and turnover numbers (when compared with previously-available methods), as well as useful levels of asymmetric induction. In addition, because of the improved reaction rates and turnover numbers, less osmium catalyst is needed in the method of the present invention than in previously-known methods. As a result, the expense and the possible toxicity problem associated with previously-known methods are reduced. Furthermore, the invention allows the recovery and reuse of osmium, which reduces the cost of the process.

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The method of the present invention is exemplified below with particular reference to its use in the asymmetric dihydroxylation of E-stilbene ( $C_6H_5CH:CHC_6H_5$ ) and trans-3-hexene ( $CH_3CH_2CH:CHCH_2CH_3$ ). The method can be  
05 generally described as presented below and that description and subsequent exemplification not only demonstrate the dramatic and unexpected results of ligand-accelerated catalysis, but also make evident the simplicity and effectiveness of the method.

10 The asymmetric dihydroxylation method of the present invention is represented by the scheme illustrated in Figure 1. According to the method of the present invention, asymmetric dihydroxylation of a selected olefin is effected as a result of ligand-accelerated catalysis.  
15 That is, according to the method, a selected olefin is combined, under appropriate conditions, with a selected chiral ligand (which in general will be a chiral substituted quinuclidine), an organic solvent, water, an oxidant and osmium tetroxide and, optionally, a compound  
20 which promotes hydrolysis of the products from the osmium. Acids or bases can be used for this purpose. In one embodiment, a selected olefin, a chiral ligand, an organic solvent, water and an oxidant are combined; after the olefin and other components are combined,  $OsO_4$  is  
25 added. The resulting combination is maintained under conditions (e.g., temperature, agitation, etc.) conducive for dihydroxylation of the olefin to occur. Alternatively, the olefin, organic solvent, chiral ligand, water and  $OsO_4$  are combined and the oxidant added to the  
30 resulting combination. These additions can occur very close in time (i.e., sequentially or simultaneously).

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In one embodiment of the present invention, components of the reaction mixture are combined, to form an initial reaction combination, and olefin is added slowly to it, generally with frequent or constant agitation, such as stirring. In this embodiment, designated the "slow addition" method, organic solvent, chiral ligand, water,  $\text{OsO}_4$  and the oxidant are combined. The olefin can then be slowly added to the other reactants. It is important that agitation, preferably stirring, be applied during the olefin addition. Surprisingly, for many, if not most olefins, slow addition of the olefin to the initial combination results in much better enantiomeric excess (ee), and a faster rate of reaction than the above-described method (i.e., that in which all the olefin is present at the beginning of the reaction). The beneficial effects (i.e., higher ee's) of slow olefin addition are shown in Table 5 (Column 6). A particular advantage of this slow-addition method is that the scope of the types of olefins to which the asymmetric dihydroxylation method can be applied is greatly broadened. That is, it can be applied to simple hydrocarbon olefins bearing no aromatic substituents, or other functional groups. In this process, the olefin is added slowly (e.g., over time), as necessary to maximize ee. This method is particularly valuable because it results in higher ee's and faster reaction times.

In another embodiment of the present method, the chiral ligands are immobilized or incorporated into a polymer, thereby immobilizing the ligands. Both monomers and polymers of alkaloid ligands can be immobilized. The immobilized ligands form a complex with the osmium catalyst, which results in formation of an osmium

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catalyst complex which can be recovered after the reaction. The  $\text{OsO}_4$ -polymer complex is recoverable and can be used for iterative processes without washing or other treatment. The complex can be recovered, for example, by filtration or centrifugation. By employing  
05 alkaloid derivatives, heterogeneous catalytic asymmetric dihydroxylation is achieved with good to excellent enantioselectivities in the dihydroxylation of olefins.

Alternatively, alkaloid polymers can be used as ligands. Alkaloid polymers which can be used are described, for example, by Kobayashi and Iwai in Tetrahedron Letters, 21:2167-2170 (1980) and Polymer Journal, 13(3):263-271 (1981); by vonHermann and Wynberg in Helvetica Chimica Acta, 60:2208-2212 (1977); and by Hodge et al., J. Chem. Soc. Perkin Trans. I, (1983) pp. 2205-  
15 2209. Both alkaloid polymer ligands and immobilized ligands form a complex with the osmium in situ. The term "polymeric", as used herein is meant to include monomers or polymers of alkaloid ligands which are chemically bonded or attached to a polymer carrier, such that the  
20 ligand remains attached under the conditions of the reaction, or ligands which are copolymerized with one or more monomers (e.g., acrylonitrile) to form a co-polymer in which the alkaloid is incorporated into the polymer, or alkaloid polymers as described above, which are not  
25 immobilized or copolymerized with another polymer or other carrier.

Industrial scale syntheses of optically active vicinal diols are possible using polymeric ligands. The convenience and economy of the process is enhanced by  
30 recycling the alkaloid- $\text{OsO}_4$  complex. This embodiment of the present method allows efficient heterogeneous

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asymmetric dihydroxylation utilizing polymeric or immobilized cinchona alkaloid derivatives.

Polymeric cinchona alkaloids which are useful in the present method can be prepared by art-recognized techniques. See, for example, Grubhofer and Schleith, Naturwissenschaften, 40:508 (1953); Yamauchi et al., Bull. Chem. Soc. Jpn., 44:3186 (1971); Yamauchi et al., J. Macromol. Sci. Chem., A10:981 (1976). A number of different types of polymers that incorporate dihydroquinidine or dihydroquinine derivatives can be used in this process. These polymers include: (a) co-polymers of cinchona alkaloid derivatives with co-polymerizing reagents, such as vinyl chloride, styrene, acrylamide, acrylonitrile, or acrylic or methacrylic acid esters; (b) cross-linked polymers of cinchona alkaloid derivatives with cross-linking reagents, such as 1,4-divinylbenzene, ethylene glycol bismethacrylate; and (c) cinchona alkaloid derivatives covalently linked to polysiloxanes. The connecting point of the polymer backbone to the alkaloid derivative can be at C(10), C(11), C(9)-O,N(1'), or C(6')-O as shown below for both quinidine and quinine derivatives. Table 3 shows the examples of the monomeric alkaloid derivatives which can be incorporated in the polymer system.

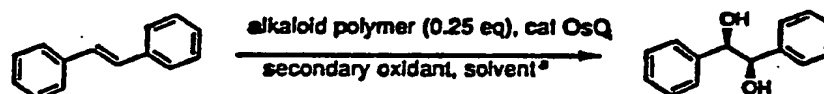
For example, a polymer binding dihydroquinidine was prepared by copolymerizing 9-(10-undecenoyl)dihydroquinidine in the presence of acrylonitrile (5 eq); a 13% yield was obtained exhibiting 4% alkaloid incorporation. This polymer, an acrylonitrile co-polymer of 9-(10-undecenoyl)-10,11-dihydroquinidine, is shown as polymer 4 in Table 1, below. Three other polymers, an acrylonitrile co-polymer of 9-(4-chlorobenzoyloxy)quinine, (polymer 1,

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Table 3) an acrylonitrile co-polymer of 11-[2-acryloyloxy)ethylsulfinyl]-9-(4-chlorobenzoyloxy)--10,11-dihydroquinine (polymer 2, Table 1) and an acrylonitrile co-polymer of 11-[2-acryloyloxy)-ethylsulfonyl]-9-(N,N-dimethylcarbamoyl)-10,11-dihydroquinidine, (polymer 3, Table 1) were prepared according to the procedures of Inaguki et al., or slightly modified versions of this procedure. See, Inaguki et al., Bull. Chem. Soc. Jpn., 60:4121 (1987). Using these polymers, the asymmetric dihydroxylation of trans-stilbene was carried out. The results are summarized in Table 1. Good to excellent asymmetric induction and reasonable reaction rates were observed. As shown in Table 1, reaction with polymer 2 exhibited the highest degree of asymmetric induction. The activity of the OsO<sub>4</sub>-polymer complex is preserved after the reaction, thus allowing repetitive use of the complex. This reaction can be carried out with terminal and aliphatically substituted olefins to show good yields and enantioselectivities (for example, styrene with polymer 2, 60% ee, 68% yield, and ethyltrans-2-octenoate with polymer 3, 60% ee, 85% yield) and the same process can be applied to a variety of different olefins.

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Table 1. Heterogeneous Catalytic Asymmetric Dihydroxylation of trans-Stilbene Using Various Polymeric Alkaloids



05	Entry	Polymers	OsO <sub>4</sub>	Secondary Oxidant	Reaction Temp	Reaction Time	Yield (%)	ee (%)
05	1	1	1 mol%	NMO	rt	7d	68	-
	2	2	1 mol%	NMO	10 °C	2-3d	81-87	85-93 <sup>b</sup>
	3	2	1 mol%	NMO	rt	24 h	81	82
	4	2	- <sup>c</sup>	NMO	rt	36 h	75	78
10	5	3	1 mol%	NMO	0 °C	48 h	85	80
	6	3	1.25 mol%	K <sub>3</sub> Fe(CN) <sub>6</sub>	rt	18 h	96	87
	7	4	1 mol%	NMO	10 °C	48 h	87	82
	8	4	1.25 mol%	K <sub>3</sub> Fe(CN) <sub>6</sub>	rt	48 h	91	86

<sup>a</sup>General procedure is set out in detail in Example 14.  
 15 With N-methylmorpholine-N-oxide (NMO) acetone/water (10/1, v/v) was the solvent and ferricyanide tert-butyl alcohol/water (1/1, v/v) was used as solvent. <sup>b</sup>Results vary slightly depending on different batches of polymer 2. <sup>c</sup>Reaction was carried out with polymer 2 which had been used in entry 3 without further addition of OsO<sub>4</sub>.

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In another embodiment of the present method, an additive which accelerates hydrolysis of the osmate ester intermediates can, optionally, be added to the reaction combination. These additives can be acids or bases, for example. Bases are preferred for this purpose. For example, soluble, carboxylic acid salts with organic-solubilizing counter-ions (e.g., tetraalkyl ammonium ions) are useful. Carboxylate salts which are preferred in the present reaction are soluble in organic media and in organic/aqueous co-solvent systems. For example, tetraethyl ammonium acetate has been shown to enhance the reaction rate and ee of some olefins (Table 5). The additive does not replace the alkaloid in the reaction. Compounds which can be used include benzyltrimethyl- ammoniumacetate, tetramethylammonium acetate and tetraethylammonium acetate. However, other oxyanion compounds (e.g., sulfonates, carbonates, borates or phosphates) may also be useful in hydrolyzing the osmate ester intermediates. The compound can be added to the reaction combination of organic solvent, chiral ligand, water and  $\text{OsO}_4$  in a reaction vessel, before olefin addition. It is important to agitate (e.g., by stirring) the reaction combination during olefin addition. The additive can also be added to the reaction combination, described above, wherein all of the olefin is added at the beginning of the reaction. In one embodiment, the amount of additive is generally approximately 2 equivalents; in general from about 1 to about 4 equivalents will be used.

In another embodiment of the present invention, the process can be run in an organic non-polar solvent such

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as toluene. This embodiment is particularly useful in the slow addition method. Preferably, a carboxylate compound which accelerates hydrolysis of the osmate ester intermediates (e.g., tetraethyl- or tetramethyl ammonium acetate) is added. This embodiment is designated the "phase transfer" method. In this embodiment olefins which are not soluble, or have limited solubility, in mixtures of acetone/water or acetonitrile/water, are dissolved in toluene and then added slowly a mixture of organic solvent, chiral ligand, water and  $\text{OsO}_4$ . The carboxylate salt serves the dual function of solubilizing the acetate ion in the organic phase where it can promote hydrolysis of the osmate ester, and carrying water associated with it into the organic phase, which is essential for hydrolysis. Higher ee's are obtained with many substrates using this method.

In a further embodiment of the present invention, a boric acid or a boric acid derivative ( $\text{R-B(OH)}_2$ , R=alkyl, aryl or OH), such as boric acid itself (i.e.,  $\text{B(OH)}_3$ ) or phenylboric acid (i.e.,  $\text{Ph-B(OH)}_2$ ), can be added to the reaction mixture. In the slow addition method, the boric acid is added to the ligand - organic solvent -  $\text{OsO}_4$  mixture prior to the addition of the olefin. The amount of boric acid added is an amount sufficient to form the borate ester of the diol produced in the reaction. Without wishing to be bound by theory, it is believed that the boric acid hydrolyzes the osmium ester and captures the diols which are generated in the reaction. Neither water nor a soluble carboxylate such as tetra-alkyl ammonium carboxylate, is required to hydrolyze the osmium ester in the present reactions. Because the presence of water can make the isolation and recovery of

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water-soluble diols difficult, the addition of a boric acid makes isolation of these diols easier. Especially, in the case of an aryl or alkyl boric acid, it is easy because, in place of the diol, the product is the cyclic borate ester which can be subsequently hydrolyzed to the diol. Iwasawa et al., Chemistry Letters, pp. 1721-1724 (1988). The addition of a boric acid is particularly useful in the slow addition method.

In another embodiment of the present method, oxidants such as potassium hexacyanoferrate (III) (potassium ferricyanide,  $K_3Fe(CN)_6$ ) is added to the reaction as a reoxidant. In a preferred embodiment, at least two equivalents of the oxidant (based on the amount of olefin substrate) is added to the reaction. It is also preferable that an equivalent amount of a base, such as potassium carbonate ( $K_2CO_3$ ), is added in conjunction with the reoxidant. High enantioselectivities are obtained in catalytic asymmetric dihydroxylations using  $K_3Fe(CN)_6$  as the reoxidant.

20 The use of potassium ferricyanide in a stoichiometric amount as an oxidant for non-asymmetric osmium-catalyzed dihydroxylation of olefins was reported by Minato, Yamamoto and Tsuji, in J. Org. Chem., 55:766 (1990). The addition of  $K_3Fe(CN)_6$  (in conjunction with  
25 the base) results in an improvement in the ability of the Tsuji's catalytic system to turn over, even in the presence of quinuclidine, a ligand which strongly inhibits catalysis when other oxidants are used, e.g. N-methylmorpholine-N-oxide (NMO). In the present  
30 embodiment, potassium ferricyanide and potassium carbonate were added to the present cinchona alkaloid-based asymmetric dihydroxylation process and the outcome,

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
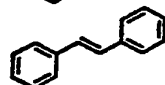
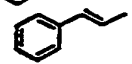
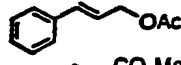
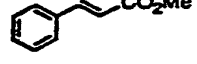

was unexpected (i.e. not just another way to reoxidize the osmium and/or achieve better turnover with difficult substrates). As shown in Table 2, the use of potassium ferricyanide/potassium carbonate in place of NMO leads to across-the-board increases in the level of asymmetric induction for most olefins. The first two columns of data shown in Table 2 are for results employing NMO with and without "slow addition" of olefin, respectively. The third column reveals the results obtained using  $K_3Fe(CN)_6$  with the same substrates and without "slow addition" of the olefin. The improvements of enantioselectivity are great as evidenced by the fact that the previous results (shown in Table 2) were obtained at 0°C while the ferricyanide experiments were performed at room temperature. The ferricyanide reactions can be run at a range of temperatures, however, depending upon the substrate.

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Table 2. Percentage enantiomeric excesses of diols obtained in the asymmetric dihydroxylation of olefins under different catalytic conditions using dihydroquinidine p-chlorobenzoate as the chiral ligand.

05

$$R-CH=CH-R' \longrightarrow \begin{array}{c} OH \\ | \\ R-CH-CH-R' \\ | \\ OH \end{array}$$

entry	olefins	NMO <sup>a</sup>		K <sub>3</sub> Fe(CN) <sub>6</sub> <sup>b</sup>
		ee(%) (slow addition)	ee(%) (no slow addition)	ee(%) (no slow addition)
1		60	56	73
10 2		95	78	99
3		86	65	91
4		79	76	91
5		86	60	95
6		69	20	74

15 <sup>a</sup>Reactions were carried out in acetone-water, 10:1 v/v, at 0°C. <sup>b</sup>Reactions were carried out in tert-butyl alcohol-water 1:1 v/v, at ambient temperature. In all cases the isolated yield was 85%-95%

20 The amount of water added to the reaction mixture is an important factor in the present method. The optimum amount of water to be added can be determined empirically and, in general, should be that amount which results in maximum ee. Generally, approximately 10 to 16 equivalents of water can be added, preferably 13 to 14

25 equivalents should be used.

An olefin of interest can undergo asymmetric dihydroxylation according to the present invention. For

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example, any hydrocarbon containing at least one carbon-carbon double bond as a functional group can be asymmetrically dihydroxylated according to the subject method. The method is applicable to any olefin of  
05 interest and is particularly well suited to effecting asymmetric dihydroxylation of prochiral olefins (i.e., olefins which can be converted to products exhibiting chirality or handedness). In the case in which the method of the present invention is used to asymmetrically  
10 dihydroxylate a chiral olefin, one enantiomer will be more reactive than the other. As a result, it is possible to separate or kinetically resolve the enantiomorphs. That is, through use of appropriately-selected reactants, it is possible to separate the asymmetrically  
15 dihydroxylated product from the unreacted starting material and both the product and the recovered starting material will be enantiomerically enriched.

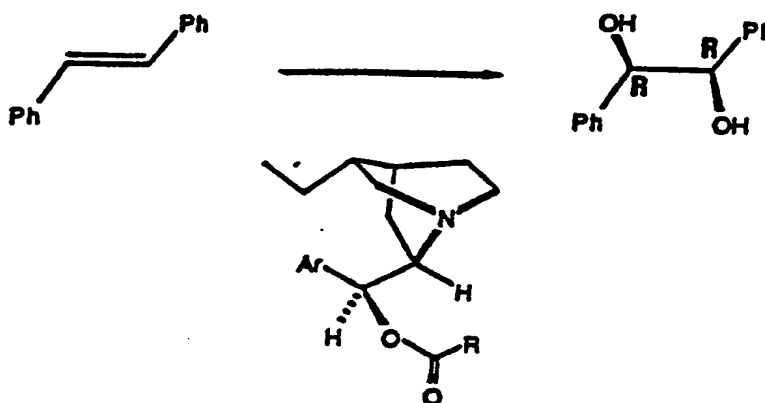
The chiral ligand used in the asymmetric dihydroxylation method will generally be an alkaloid, or a basic  
20 nitrogenous organic compound, which is generally heterocyclic. The chiral ligand can be a naturally occurring compound, a purely synthetic compound or a salt thereof, such as a hydrochloride salt. The optimum derivative which is used can be determined based upon the  
25 process conditions for each reaction. Examples of alkaloids which can be used as the chiral ligand in the asymmetric dihydroxylation method include cinchona alkaloids, such as quinine, quinidine, cinchonine, and cinchonidine. Examples of alkaloid derivatives useful in  
30 the method of the present invention are shown in Table 3. As described in detail below, the two cinchona alkaloids quinine and quinidine act more like enantiomers than like diastereomers in the scheme represented in Figure 1.

-20-

As represented in Figure 1, and as shown by the results in Table 4, dihydroquinidine derivatives (represented as DHQD) and dihydroquinine derivatives (represented as DHQ) have a pseudo-enantiomeric relationship in the present method (DHQD and DHQ are actually diastereomers). That is, they exhibit opposite enantiofacial selection. Such derivatives can be, for example, esters or ethers, although other forms can be used. The choice of derivative depends upon the process. When dihydroquinidine is used as the ligand, delivery of the two hydroxyl groups takes place from the top or upper face (as represented in Figure 1) of the olefin which is being dihydroxylated. That is, in this case direct attack of the re- or re,re- face occurs. In contrast, when the dihydroquinine derivative is the ligand used, the two hydroxyl groups are delivered from the bottom or lower (si- or si,si-face) face of the olefin, again as represented in Figure 1. This is best illustrated by reference to entries 1, 2 and 5 of Table 4. As shown, when DHQD (dihydroquinidine esters) is used, the resulting diol has an R or R,R configuration and when ligand 2 (dihydroquinine esters) is used, the resulting diol has an S or S,S configuration.

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Table 3 Alkaloid Derivatives



	R	Dihydroquinidine Derivative	Yield (%)	%ee
05	3-ClC <sub>6</sub> H <sub>4</sub>	3-chlorobenzoyl	89	96.5
	2-MeOC <sub>6</sub> H <sub>4</sub>	2-methoxybenzoyl	89	96
	3-MeOC <sub>6</sub> H <sub>4</sub>	3-methoxybenzoyl	87	96.7
	2-C <sub>10</sub> H <sub>7</sub>	2-naphthoyl	95.4	98.6
	C <sub>6</sub> H <sub>11</sub>	cyclohexanoyl	90	91
10	4-PhC <sub>6</sub> H <sub>4</sub>	4-phenylbenzoyl	89	96
	2,6-(MeO) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	2,6-dimethoxy- benzoyl	88	92
	4-MeOC <sub>6</sub> H <sub>4</sub>	4-methoxybenzoyl	91	97.6
	4-ClC <sub>6</sub> H <sub>4</sub>	4-chlorobenzoyl	93	99
	2-ClC <sub>6</sub> H <sub>4</sub>	2-chlorobenzoyl	87	94.4
15	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	4-nitrobenzoyl	71	93
	C <sub>6</sub> H <sub>5</sub>	benzoyl	92	98

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Table 3 cont.

	Me <sub>2</sub> N	dimethyl-carbamoyl	96	95
	Me	acetyl	72	94
	MeOCH <sub>2</sub>	α-methoxyacetyl	66	93
05	AcOCH <sub>2</sub>	α-acetoxyacetyl	96	82.5
	Me <sub>3</sub> C	trimethylacetyl	89	86.5




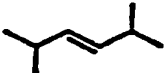
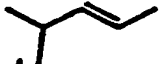
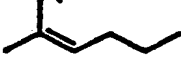

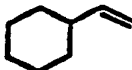
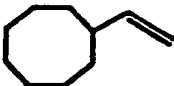


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The example below is a phosphoryl derivative and therefore differs from the carboxylic acid ester derivatives shown above: the phosphorus atom is directly bound to the oxygen atom of the alkaloid.

10	Ph <sub>2</sub> P(O)	diphenylphosphinic ester	69	97.5
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Table 4

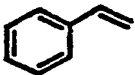
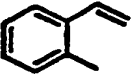
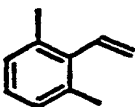
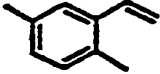
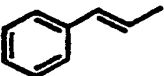
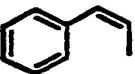
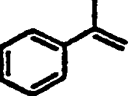
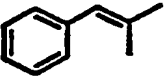
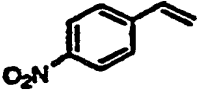
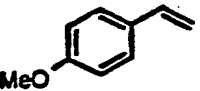
	Olefins	ligand; ee <sup>a</sup> ; confgn. of diol
		DHQD; 20%, (70%, 10h); RR DHQ; (60%, 16h); SS
05		DHQD; (70%, 120h)
		DHQD; (69%, 30h); RR DHQ; (63%, 30h); SS
		DHQD; 12%, (46%, 24h), (76%, 24h + 1 eq OAc)
		DHQD; 37.5%
		DHQD; (46%, 24h, rt)
10		DHQD; (40%, 24h, rt)
		DHQD; 46%, (50%, 20h); R
		DHQD; 50%
		DHQD; 40%
		DHQD; 35%, (40%, 12h)

15

<sup>a</sup> Enantiomeric excesses in parentheses were obtained with slow addition of olefin over a period of time indicated and with stirring at 0°C except otherwise stated. Tetraethylammonium acetate tetrahydrate were added in some cases as indicated.

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Table 4 cont.

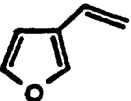
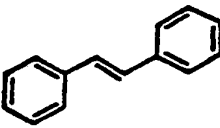
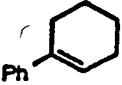
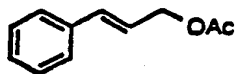
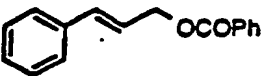
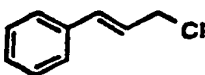
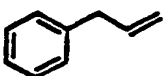
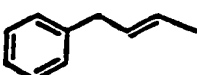
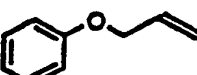
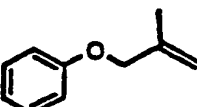
Olefins	ligand; ee <sup>a</sup> ; confgn. of diol
	DHQD; 56%, (61%, 5h); R DHQ; 54%; S
05 	DHQD; 53%
	DHQD; 65%
	DHQD; 63%
	DHQD; 65%, (86%, 5h); RR DHQ; 55%, (80%, 5h); SS
	DHQD; 0-10%
10 	DHQD; 33%; R
	DHQD; 34%, (53%, 24h)
	DHQD; 51%
	DHQD; 67%

<sup>a</sup> Enantiomeric excesses in parentheses were obtained with slow addition of olefin over a period of time indicated and with stirring at 0°C except otherwise stated. Tetraethylammonium acetate tetrahydrate were added in some cases as indicated.

15

- 25 -

Table 4 cont

	Olefins	ligand; ee <sup>a</sup> ; confgn. of diol
		DHQD; 40%
05		DHQD; 80%; 92% in the presence of 2 eq. OAc; RF DHQ; 79%; SS
		DHQD; 10%, (78%, 26h), (81%, 16h + 1eq OAc) DHQ; (73%, 26h)
		DHQD; 76%; RR
		DHQD; 80%
		DHQD; 60%, (78%, 10h)
10		DHQD; 20%
		DHQD; (44%, 10h)
		DHQD; 34%
		DHQD; 27%

<sup>a</sup> Enantiomeric excesses in parentheses were obtained with slow addition of olefin over a period of time indicated and with stirring at 0°C except otherwise stated. Tetraethylammonium acetate tetrahydrate were added in some cases as indicated.

- 26 -

Table 4 cont

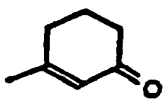
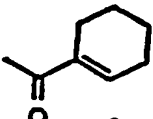
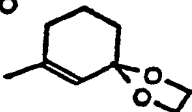
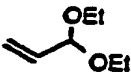

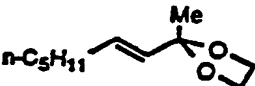
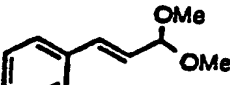
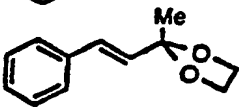
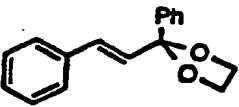
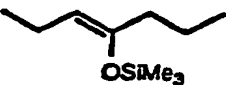
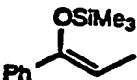
Olefins	ligand; ee <sup>a</sup> ;
	DHQD; 38%
	DHQD; 47.4%, (67%, 31h)
	DHQD; 53%
	DHQD; 45%
	DHQD; (52% de, 31h)
	DHQD; (70% de, 42h)
	DHQD; 74.3%
	DHQD; (36%, 24h + OAc, rt)
	DHQD; 92%
	DHQD; 91%
	DHQD; 80-85%
	DHQD; <60%, (80%, slow addition)
	DHQD; (38%, toluene-water, 24h + OAc, rt)

15

<sup>a</sup> Enantiomeric excesses in parentheses were obtained with slow addition of olefin over a period of time indicated and with stirring at 0°C except otherwise stated. Tetraethylammonium acetate tetrahydrate were added in some cases as indicated.

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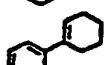


Table 4 cont

Olefins	ligand; ee <sup>a</sup> ;
	DHQD; (10%, 24h, rt)
	DHQD; (36%, 24h + OAc, rt)
	DHQD; (37%, 12h + OAc)
	DHQD; 27%, (31%, 13h)
	DHQD; (56%, 20h) (66%, 20h + OAc)
	DHQD; (46%, 18h) (50%, 18h + OAc)
	DHQD; (75%, 18h) (83%, 18h + OAc)
	DHQD; (60%, 10h) (89%, 10h + OAc)
	DHQD; (85%, 20h) (87%, 20h + OAc)
	DHQD; (27%, 23h + OAc)
	DHQD; (72%, 23h) (78%, 23h + OAc)

<sup>a</sup> Enantiomeric excesses in parentheses were obtained with slow addition of olefin over a period of time indicated and with stirring at 0 °C except otherwise stated. Tetraethylammonium acetate tetrahydrate were added in some cases as indicated.

Table 5

Enantiomeric excesses obtained in the asymmetric dihydroxylation of  
olefins under different conditions

entry	olefin	stoichiometric <sup>a</sup>	catalytic <sup>b</sup> (original)	catalytic <sup>c</sup> (acetate)	catalytic <sup>d</sup> (slow addition)
1		61	56	61	60 (5 h)
2		87	65	73	86 (5h)
3		79	8 <sup>e</sup>	52	78 (26 h) <sup>f</sup>
4		80	12 <sup>g</sup>	61	46 (24 h) <sup>h</sup> 76 (24 h + OAc)
5		69	20	64	70 (10 h)

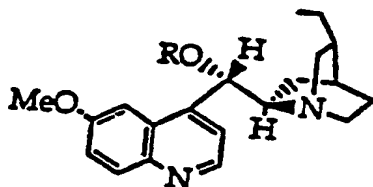
<sup>a</sup>All stoichiometric reactions were carried out in acetone-water, 10:1 v/v, at 0 °C and at a concentration of 0.15 M in each reagent. <sup>b</sup>All reactions were carried out at 0 °C according to the original procedure reported in ref. 1(a). <sup>c</sup>All reactions were carried out exactly as described in ref. 1(a) (i.e. without slow addition) except that 2 eq of Et<sub>4</sub>NOAc·4H<sub>2</sub>O were present. <sup>d</sup>All reactions were carried out at 0 °C as described in note 2 for *trans*-3-hexene with an alkaloid concentration of 0.25 M. The period for slow addition of the olefin is indicated in parentheses. The ee's shown in the Table were obtained with dihydroquinidine *p*-chlorobenzoate as the ligand. Under the same conditions, the pseudoenantiomer, dihydroquinine *p*-chlorobenzoate, provides products with ee's 5-10% lower. In all cases the isolated yield was 85-95%. <sup>e</sup>This reaction took 7 days to complete. <sup>f</sup>With an addition period of 16 h, ee's of 63 and 65% were obtained at 0 °C and 20 °C, respectively; with the combination of slow addition over a period of 16 h and the presence of 1 eq of Et<sub>4</sub>NOAc·4H<sub>2</sub>O at 0°C, an ee of 81% was realized. <sup>g</sup>This reaction took 5 days to complete. <sup>h</sup>When the reaction was carried out at 20 °C and the olefin was added over a period of 24 h, an ee of 59% was obtained.

-29-

Because of this face selection rule or phenomenon, it is possible, through use of the present method and the appropriate chiral ligand, to pre-determine the absolute configuration of the dihydroxylation product.

05 As is also evident in Table 4, asymmetric dihydroxylation of a wide variety of olefins has been successfully carried out by means of the present invention. Each of the embodiments described results in asymmetric dihydroxylation, and the "slow addition" method is particularly useful for this purpose. In each  
10 of the cases represented in the Table in which absolute configuration was established, the face selection "rule" (as interpreted with reference to the orientation represented in Figure 1) applied: use of DHQD resulted  
15 in attack or dihydroxylation occurring from the top or upper face and use of DHQ resulted in attack or dihydroxylation occurring from the bottom or lower face of the olefin. This resulted, respectively, in formation of products having an R or R,R configuration and products  
20 having an S or S,S configuration.

In a preferred embodiment of the present method, aromatic ethers of various cinchona alkaloids are used as  
ligands. The term "aromatic ethers" includes aryl ethers and heterocyclic ethers. A high level of asymmetric  
25 induction can be obtained using aromatic ethers of dihydroquinidine or dihydroquinine as ligands. For example, aromatic ethers having the following formula are particularly useful:



-30-

wherein R is phenyl, naphthyl, or o-methoxyphenyl. The stoichiometric asymmetric dihydroxylation of various dialkyl substituted olefins was performed using the phenyl ether derivative of dihydroquinidine. The results are shown in Table 6.

Table 6. Stoichiometric Asymmetric Dihydroxylation Phenyl Ether Dihydroquinidine

Entry	Olefins	Reaction temp (°C)	%ee <sup>a</sup>	%ee <sup>a</sup> with 3 (for comparison)
10	1	0	85	71
	2	-78	95	
	3	0	88	73
	4	-78	93	
15	5	0	89	79
	6	-78	94	
	7	0	90	67
	8	0	97 <sup>c</sup>	77 <sup>c</sup>

<sup>a</sup> Enantiomeric excess was determined by GLC or HPLC analysis of the bis-Mosher ester derivatives. <sup>b</sup> The reaction was worked up with NaHSO<sub>3</sub> in H<sub>2</sub>O-THF. <sup>c</sup> Diastereomeric excess.

The reaction was performed by adding 1 eq of olefin to a 1:1 mixture of OsO<sub>4</sub> and the ligand in dry toluene (0.1M) followed by a reductive work-up using lithium aluminum hydride (LiAlH<sub>4</sub>) to yield the (R,R)-diol in

-31-

60-95% yield with good to excellent enantiomeric excess. Reactions with  $\alpha,\beta$ -unsaturated esters also proceeded with much improved enantio- and diastereoselectivities ( $\geq 90\%$ , as shown in entries 7 and 8, Table 6) using this ligand.

05 By lowering the reaction temperature to  $-78^\circ\text{C}$ , the reaction with straight chain dialkyl substituted olefins proceeded with very high enantioselectivities ( $\geq 93\%$ , as shown in entries 2, 4 and 6 of Table 6). In the several cases which were plotted the variance in ee with temper-

10 ature closely followed the Arrhenius relationship.

Several dihydroquinidine aromatic ether derivatives were examined as chiral ligands for the asymmetric dihydroxylation of (E)-3-hexene, as shown in Table 7, below. Reactions with all of the aromatic ether

15 derivatives tried exhibited higher enantioselectivities than the corresponding reaction with p-chlorobenzoate dihydroquinidine. The highest enantioselectivity was obtained with 9-O-(2'-methoxyphenyl)-dihydroquinidine (entry 2, Table 7).

- 32 -

Table 7. Stoichiometric Asymmetric Hydroxylation of (E)-3-hexene

Entry	1	2	3	4	5
05 R					
%ee	85	88	81	76	75

In one embodiment of the present method, aromatic ether ligands were used in the catalytic asymmetric dihydroxylation of (E)-3-hexene. In this embodiment, the results are summarized in Table 8. The catalytic asymmetric dihydroxylation reactions (entries 1-3, Table 8) were carried out by slow addition of (E)-3-hexene (1 eq) to a mixture of phenyl ether dihydroquinidine (0.25 eq), N-methylmorpholine N-oxide (NMO, 1.5 eq) and  $\text{OsO}_4$  (0.004 eq) in acetone-water (10/1, v/v) at 0°C, followed by work-up with  $\text{Na}_2\text{S}_2\text{O}_5$ . The reaction proceeded faster

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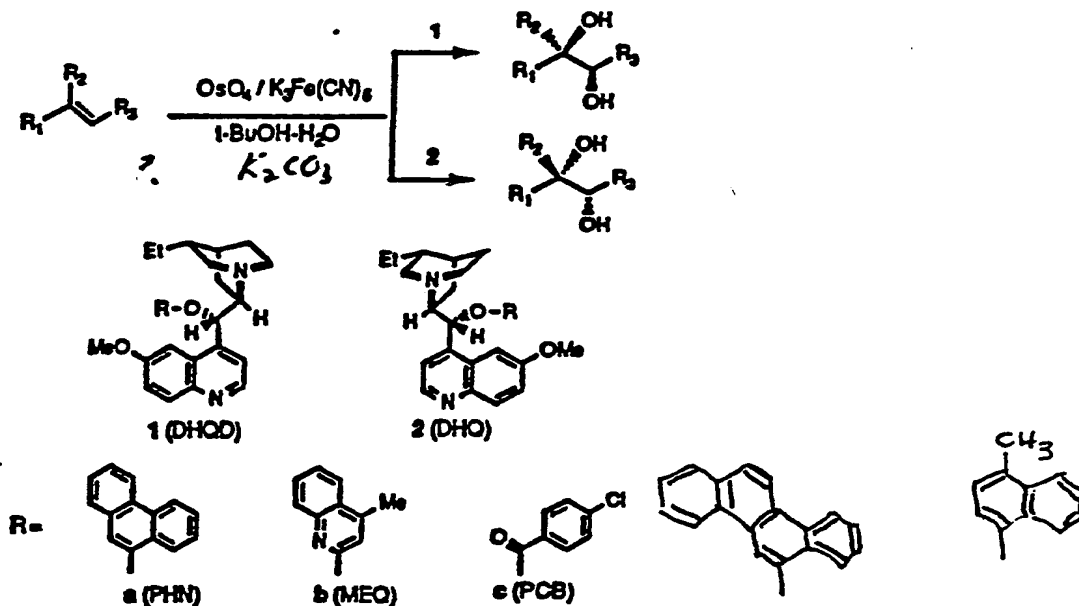
upon addition of tetraethylammonium acetate (2 eq) to the reaction mixture (entry 4, Table 8). Potassium ferricyanide was added as the secondary oxidant (entries 5 and 6, Table 8). In these cases, slow addition of olefin was not required. To a mixture of (E)-3-hexene (1 eq), aromatic ether of dihydroquinidine (0.25 eq),  $K_3Fe(CN)_6$  (3eq) and potassium carbonate ( $K_2CO_3$  3 eq) in tert-butyl alcohol-water (1/1, v/v) was added  $OsO_4$  (0.0125 eq); the resulting mixture was stirred at room temperature for 20 hours. Reductive work-up (with  $Na_2SO_3$ ) gave the diol in 85-90% yield with essentially the same ee as that obtained in the stoichiometric reaction.

Table 8. Catalytic Asymmetric Dihydroxylation of (E)-3-hexene

Entry	Ligand	$OsO_4$	Secondary oxidant	Additive	Reaction Temp (°C)	Reaction Time (hr)	%ee
1	1	0.4mol%	NMO		0	16	70
2	1	0.4	NMO		0	30	75
20 3	1	0.4	NMO		0	120	85
4	1	0.4	NMO	$Et_4NOAc$	0	16	82
5	1	1.25	$K_3Fe(CN)_6$	$K_2CO_3$	rt	20	83
6	2	1.25	$K_3Fe(CN)_6$	$K_2CO_3$	rt	20	89

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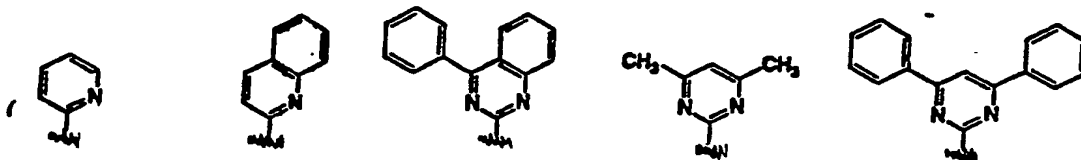
Enantioselectivities in the dihydroxylation of dialkyl substituted olefins, which were previously only possible through the use of stoichiometric reagents at low temperature, can now be obtained in the catalytic asymmetric dihydroxylation using these aromatic ether ligands at room temperature. Disclosed here are two ligands which are particularly useful in the present method: the 9-O-(9'-phenanthryl) ethers and the 9-O-(4'-methyl-2'-quinolyl) ethers of dihydroquinidine (1a and 1b below) and dihydroquinine (2a and 2b below).



The R group can include other benzenoid hydrocarbons. The aromatic moieties also can be modified by substitutions such as by lower alkyl, alkoxy or halogen radical groups.

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Additional effective heterocyclic aromatic ligands include:



05      The improvements achieved with these new ligands are best appreciated through the results shown in Table 9. A particularly important advantage is that the terminal olefins (entries 1-7, Table 9), have moved into the "useful" ee-range for the first time.

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Table 9. Ee (%)<sup>a</sup> of the Diols Resulting from Catalytic Asymmetric Dihydroxylation<sup>b</sup>

class of olefin	entry	olefin	temp, °C	1a (PHN)	1b (MEQ)	1c (PCB)	config <sup>d</sup>
	1		0	74	65	45°	R
	2		0	93	85	64°	(R)
	3		0	79	79	44°	R
	4		0	78	87	74°	R
	5		0	83	93	88°	R
	6		0	82	73	37°	R
	7		0	69	88	74°	(R)
	8		rt	96	90	79	R,R
	9		rt	94	85	67	2S,3R
	10		rt	98	98	91	2S,3R
	11		rt	99	98	99	R,R
	12		rt	86	81	74	R
	13		rt	93	92	91	R,R

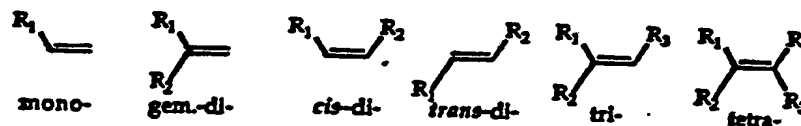
Enantiomeric excess as were determined, by HPLC, GC, or <sup>1</sup>H-NMR analysis of the bis-MTPA esters (see supplementary materials for details of analyses). <sup>b</sup>All reactions were performed essentially as described in Example 20 with some variations: (1) 1-1.25 mol % OsO<sub>4</sub> or

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05  $K_2OsO_2(OH)_4$ ; (2) 2-25 mol.% ligand, (3) 0.067-0.10 M in  
olefin; (4) 18-24 h reaction time. In all cases the  
isolated yield of the diol was 75-95%. <sup>c</sup>All olefins are  
commercially available except entries 6 and 7. <sup>8</sup>The  
absolute configurations of the diols were determined by  
comparison of their optical rotations with literature  
values (entries 1, 3-5, 8, 10-13), or with an authentic  
diol (R)-(-)-2-phenyl-1,2-propanediol (entry 6), <sup>10</sup> or by  
10 comparison of ORD (entry 9). <sup>11</sup>The remaining two  
(entries 2,7) are tentatively assigned by analogy from  
optical rotations of closely related diols and the  
retention times of the bis MTPA esters on HPLC (see  
supplementary material for details). <sup>e</sup>Reaction was  
15 carried out at room temperature.

The data for the new ligands 1a and 1b has been  
compared to the results for another ligand, the *p*-chloro-  
benzoate 1c (last column of Table 9). Note further that  
the highest enantioselectivities for each substrate have  
20 been highlighted by bracketing, and that this bracketing  
is conspicuously sparse in the column under ligand 1c.  
Clearly, ligands 1a and 1b also deliver a significant ee  
enhancement for trans-substituted olefins, especially  
those lacking aromatic substituents (entries 8 and 9).

25 The six possible substitution patterns for olefins  
are:



Four of these classes are represented in Table 9.  
30 The present success with the mono- and gem-disubstituted  
types has essentially doubled the scope of the catalytic  
ADH when compared to diol production when ligands other  
than aromatic ether ligands are used.

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Strikingly absent from Table 9 are the results for the dihydroquinine ligand analogs (i.e., 2a, 2b and 2c). The quinidine and quinine analogs of these new ligands also give very good results with the same olefin classes shown in Table 9. Like the original *p*-chlorobenzoate ligand comparison (1c vs 2c),<sup>2b</sup> the quinine ether series gives somewhat lower ee's than their dihydroquinidine counterparts (1a vs 2a and 1b vs 2b). For example, vinyl cyclooctane (entry 2) gives the S-diol in 8.8% ee using 2a compared with the R-diol in 93% ee recorded in Table 9 using 1a.






The detailed general procedure for the catalytic ADH is given in note Example 20, using ligand 1a and vinyl cyclooctane as the substrate. Note the experimental simplicity of the process. I is performed in the presence of air and water at either ambient or ice bath temperature. A further advantage is that the most expensive component, the ligand, can be easily recovered in >80% yield.

Note also that the solid and nonvolatile osmium (VI) salt,  $K_2OsO_2(OH)_4$ , is used in place of osmium tetroxide. This innovation should be useful in all catalytic oxidations involving  $OsO_4$  since it avoids the risk of exposure to volatile osmium species.

Another olefin class can be asymmetrically dihydroxylated when O-carbamoyl-, *p*-chlorobenzoate- or O-phenanthroline- substitutions of DHQD or DHQ ligands are used in the method of the present invention. This class is the cis-disubstituted type of olefin. Table 10 shows the ee's and % yields for a variety of substrates when these ligands were used. Procedures for producing these ligands and for carrying out the ADH are illustrated in Examples 23 and 24.

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Table 10: Enantiomeric Excesses (ee's) Obtained for cis-Olefins with Various Dihydroquinidine Ligands; ee (% yield)

05	Substrate:					
	Ligand:					
	DMC-O-DHQD	20(68)	17(71)	4(78)	4(66)	17(66)
	MPC-O-DHQD	46(82)	0(54)	6(100)	6(90)	49(47)
	DPC-O-DHQD	44(85)	10(37)	0(100)	3(70)	44(75)
	PCB-O-DHQD	35(92)	2(80)	19(83)	4(75)	24(63)
10	PHN-O-DHQD	22( )	4(78)	37(89)	7(75)	-23(56)
	PhC-O-DHQD	17(86)	12(69)	14(84)	0(89)	10(82)

where the ligands are ether linked substituents of DHQD designated as dimethyl carbamoyl (DMC), methyl phenyl carbomoyl (MPC), diphenylcarbamoyl (DPC),  
 15 p-chlorobenzoate (PCB), phenanthryl (PHN) and phenyl carbomoyl (PhC).

The greatest ee's were obtained when  
 O-carbamoyl-DHQD ligands were employed which indicates  
 that this class of compound is an attractive ligand for  
 20 asymmetric dihydroxylation of the cis-disubstituted type  
 of olefin. These results also demonstrate that  
 reasonably good yields and ee's can be obtained for this

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olefin class and that, now, five of the six classes of olefins can successfully be asymmetrically dihydroxylated.

In general, the concentration of the chiral ligand used will range from approximately 0.001 M or less to 2.0 M. In one embodiment, exemplified below, the solution is 0.261M in alkaloid 1 (the dihydroquinidine derivative). In one embodiment of the method, carried out at room temperature, the concentrations of each alkaloid represented in Figure 1 is at 0.25M. In this way, the enantiomeric excess resulting under the conditions used is maximized. The amount of chiral ligand necessary for the method of the present invention can be varied as the temperature at which the reaction occurs varies. For example, it is possible to reduce the amount of alkaloid (or other chiral ligand) used as the temperature at which the reaction is carried out is changed. For example, if it is carried out, using the dihydroquinidine derivative, at 0°C, the alkaloid concentration can be 0.15M. In another embodiment, carried out at 0°C, the alkaloid concentration was 0.0625M.

Many oxidants (i.e., essentially any source of oxygen) can be used in the present method. For example, amine oxides (e.g., trimethyl amine oxides), tert-butyl hydroperoxide, hydrogen peroxide, and oxygen plus metal catalysts (e.g., copper ( $\text{Cu}^+ - \text{Cu}^{++}/\text{O}_2$ ), platinum ( $\text{Pt}/\text{O}_2$ ), palladium ( $\text{Pd}/\text{O}_2$ ) can be used. Alternatively,  $\text{NaOCl}$ ,  $\text{KIO}_4$ ,  $\text{KBrO}_3$  or  $\text{KClO}_3$  can be used. In one embodiment of the invention, N-methylmorpholine N-oxide (NMO) is used as the oxidant. NMO is available commercially (e.g., Aldrich Chemicals, 97% NMO anhydrous, or as a 60%

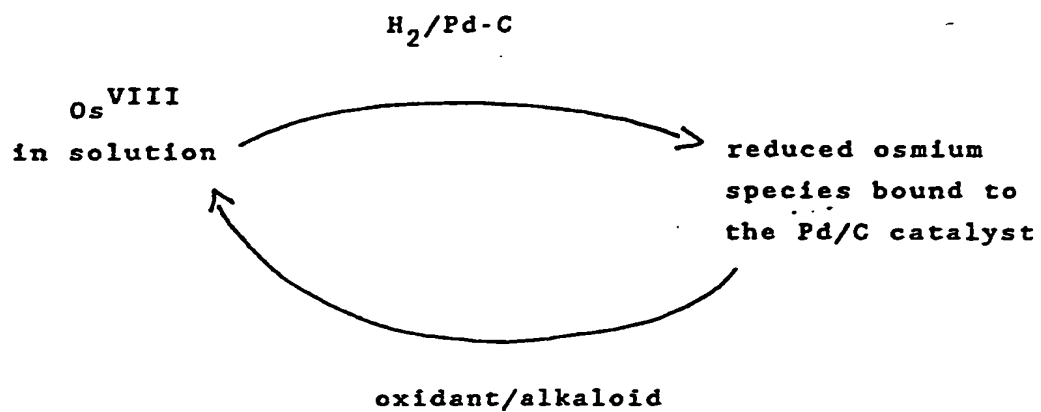
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solution in water). In addition, as stated above, potassium ferricyanide can be used in lieu of the amine oxide. Potassium ferricyanide is an efficient oxidant in the present method.

05 Osmium will generally be provided in the method of the present invention in the form of osmium tetroxide ( $\text{OsO}_4$ ) or potassium osmate VI dihydrate, although other sources (e.g., osmium trichloride anhydrous, osmium trichloride hydrate) can be used.  $\text{OsO}_4$  can be added as a  
10 solid or in solution.

The osmium catalyst used in the method of the present invention can be recycled, for re-use in subsequent reactions. This makes it possible not only to reduce the expense of the procedure, but also to recover  
15 the toxic osmium catalyst. For example, the osmium catalyst can be recycled as follows: Using reduction catalysts (e.g., Pd-C), the osmium VIII species is reduced and adsorbed onto the reduction catalyst. The resulting solid is filtered and resuspended. NMO (or an  
20 oxidant), the alkaloid and the substrate (olefin) are added, with the result that the osmium which is bound to the Pd/C solid is reoxidized to  $\text{OsO}_4$  and re-enters solution and plays its usual catalytic role in formation of the desired diol. This procedure (represented below)  
25 can be carried out through several cycles, thus re-using the osmium species. The palladium or carbon can be immobilized, for example, in a fixed bed or in a cartridge.

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In one embodiment an olefin, such as recrystallised trans-stilbene ( $C_6H_5CH:CHC_6H_5$ ), is combined with a chiral ligand (e.g., p-chlorobenzoyl hydroquinidine), acetone, water and NMO. The components can be added sequentially or simultaneously and the order in which they are combined can vary. In this embodiment, after the components are combined, the resulting combination is cooled (e.g., to approximately  $0^{\circ}C$  in the case of trans-stilbene); cooling can be carried out using an ice-water bath.  $OsO_4$  is then added (e.g., by injection), in the form of a solution of  $OsO_4$  in an organic solvent (e.g., in toluene). After addition of  $OsO_4$ , the resulting combination is maintained under conditions appropriate for the dihydroxylation reaction to proceed.

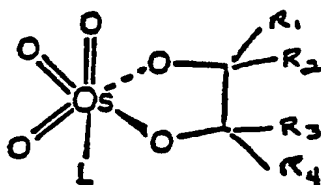
In another preferred embodiment, a chiral ligand (e.g., dihydroquinidine 4-chlorobenzoate), NMO, acetone, water and  $OsO_4$  (as a 5M toluene solution) are combined. The components can be added sequentially or simultaneously and the order in which they are combined can vary. In this embodiment, after the components are combined, the resulting combination is cooled (e.g., to approximately  $0^{\circ}C$ ); cooling can be carried out using an ice-water bath. It is particularly preferred that the combination is agitated (e.g., stirred). To this well-stirred mixture, an olefin (e.g., trans-3-hexene) is added slowly (e.g., by injection). The optimum rate of addition (i.e., giving maximum ee), will vary depending on the nature of the olefinic substrate. In the case of trans-3-hexene, the olefin was added over a period of about 16-20 hours. After olefin addition, the mixture can be stirred for an additional period of time at the

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low temperature (1 hour in the case of trans-3-hexene). The slow-addition method is preferred as it results in better ee and faster reaction times.

05 In another embodiment, a compound which accelerates hydrolysis of the osmate ester intermediates (e.g., a soluble carboxylate salt, such as tetraethylammonium acetate) is added to the reaction mixture. The compound (approximately 1-4 equiv.) can be added to the mixture of  
10 chiral ligand, water, solvent, oxidant and osmium catalyst and olefin, or prior to the addition of olefin, if the olefin slow-addition method is used.

The diol-producing mechanistic scheme which is thought to operate when the slow-addition of olefin method is used is represented in Figure 4. According to  
15 the proposed mechanism, at least two diol-producing cycles exist. As shown in Figure 4, only the first cycle appears to result in high ee. The key intermediate is the osmium (VIII) trioxoglycolate complex, shown as formula 3 in Figure 4, which has the following general  
20 formula:



25 wherein L is a chiral ligand and wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> and R<sub>4</sub> are organic functional groups corresponding to the olefin. For example, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> and R<sub>4</sub> could be alkyl,

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aryl, alkoxy aryloxy or other organic functional groups compatible with the reaction process. Examples of olefins which can be used, and their functional groups, are shown on Table 4 hereinabove.

05        This complex occupies the pivotal position at the junction between the two cycles, and determines how diol production is divided between the cycles.

         Evidence in favor of the intermediacy of the osmium (VIII) trioxoglycolate complex (formula 3, Figure 4) is  
10        provided by the finding that the events in Figure 4 can be replicated by performing the process in a stepwise manner under stoichiometric conditions. These experiments were performed under anhydrous conditions in toluene. In the process shown in Figure 4, one equivalent  
15        of the alkaloid osmium complex (shown as formula 1, Figure 4) is allowed to react with an olefin to give the emerald green monoglycolate ester (formula 2, Figure 4). A different olefin is then added, followed by an equivalent of an anhydrous amine N-oxide, and rapid formation  
20        of the bisglycolate ester (formula 4, Figure 4) is observed. Upon reductive hydrolysis of the bisglycolate ester, precisely one equivalent of each diol is liberated. These experiments indicate that a second cycle, presumably via the osmium trioxoglycolate complex, is as  
25        efficient as the first in producing diols from olefins. One can also use the same olefin in both steps to run this tandem addition sequence. When this was done using 1-phenylcyclohexene as the olefin, the ee for the first step was 81% and the ee for the second step was 7% in the  
30        opposite direction (i.e., in favor of the minor enantiomer in the first step). Thus, for this substrate

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any intrusion of the second cycle is particularly damaging, and under the original catalytic conditions 1-phenylcyclohexene only gave 8% ee (entry 3, Table 5).

Reduced ee is just part of the counterproductivity of turning on the second cycle; reduced turnover is the other liability. The bisosmate esters (formula 4, Figure 4) are usually slow to reoxidize and hydrolyze, and therefore tend to tie up the catalyst. For example, 1-phenylcyclohexene took 7 days to reach completion under the original conditions (the 8% ee cited above). With slow addition of the olefin, the oxidation was complete in one day and gave the diol in 95% yield and 78% ee (entry 3, Table 5).

The most important prediction arising from the mechanistic scheme shown in Figure 4 is the minimization of the second cycle if the olefin is added slowly. Slow addition of the olefin presumably gives the osmium (VIII) trioxoglycolate intermediate sufficient time to hydrolyze so that the osmium catalyst does not get trapped into the second cycle by reacting with olefin. To reiterate, the second cycle not only ruins the ee but also impedes turnover, since some of the complexes involved are slow to reoxidize and/or hydrolyze. The optimum feed rate depends on the olefin; it can be determined empirically, as described herein.

The maximum ee obtainable in the catalytic process is determined by the addition of the alkaloid osmium complex (formula 1, Figure 4) to the olefin (i.e., the first column in Table 5). Thus, stoichiometric additions can be used to enable one to determine the ee-ceiling which can be reached or approached in the catalytic

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process if the hydrolysis of 3 (Figure 4) can be made to dominate the alternative reaction with a second molecule of olefin to give 4 (Figure 4). In the case of terminal olefins, styrene (Table 5), the trioxoglycolate esters hydrolyze rapidly, since slow addition, or the effect of the osmate ester hydrolytic additive give only a slight increase in the ee. However, most olefins benefit greatly from any modification which speeds hydrolysis of the osmate ester intermediate (3, Figure 4) (entries 2-5, Table 5), and in extreme cases neither the effect of the osmate ester-hydrolytic additive nor slow addition is sufficient alone. Diisopropyl ethylene (entry 4, Table 5) approaches its ceiling-ee only when both effects are used in concert, with slow addition carried out in the presence of acetate. The other entries in the Table reach their optimum ee's through slow addition alone, but even in these cases the addition times can be substantially shortened if a compound, such as a tetraalkyl ammonium acetate, is present.

In many cases, temperature also affects the ee. When the ee is reduced by the second cycle, raising the temperature can often increase it. This occurs, in particular, when NMO is used as the secondary oxidant. For example, diisopropyl ethylene gave 46% ee at 0°C and 59% ee at 25°C (24h slow addition time in both cases). The rate of hydrolysis of the osmium trioxoglycolate intermediate is apparently more temperature dependent than the rate of its reaction with olefin. This temperature effect is easily rationalized by the expected need to dissociate the chiral ligand from the osmium complex (3) in order to ligate water and initiate

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hydrolysis, but the ligand need not dissociate for addition of olefin to occur (in fact this second cycle olefin addition step is also likely to be ligand-accelerated).

05       When  $K_3Fe(CN)_6$  is used as the secondary oxidant, the effect of temperature on the ee is opposite the effect when NMO is the secondary oxidant. That is, lowering the temperature can often increase the ee when potassium ferricyanide is the secondary oxidant. Also, the olefin  
10       need not be slowly added to the mixture but can, instead, be added all at once when potassium ferricyanide is the secondary oxidant. These effects and conditions  
15       apparently occur because the second cycle is suppressed when this secondary oxidant is used. The reactions of the second cycle do not appreciably contribute to the formation of diols when the secondary oxidant is potassium ferricyanide.

      The following is a description of how optimum conditions for a particular olefin can be determined. To  
20       optimize the osmium-catalyzed asymmetric dihydroxylation:  
1) If from the known examples there is doubt about what the ceiling-ee is likely to be, it can be determined by performing the stoichiometric osmylation in acetone/water at 0°C using one equivalent of the  $OsO_4$  - alkaloid  
25       complex; 2) Slow addition at 0°C: the last column in Table 3 can be used as a guide for choosing the addition time, bearing in mind that at a given temperature each olefin has its own "fastest" addition rate, beyond which the ee suffers as the second cycle turns on. When the  
30       olefin addition rate is slow enough, the reaction mixture remains yellow-orange (color of 1, Figure 4); when the

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rate is too fast, the solution takes on a blackish tint, indicating that the dark-brown-to-black bisglycolate complex (4, Figure 4) is being generated; 3) If the ceiling ee is not reached after steps 1 and 2, slow  
05 addition plus tetraalkyl ammonium acetate (or other compound which assists hydrolysis of the osmate ester intermediate) at 0°C can be used; 4) slow addition plus a soluble carboxylate salt, such as tetraalkyl ammonium acetate at room temperature can also be used. For all  
10 these variations, it is preferable that the mixtures is agitated (e.g., stirred) for the entire reaction period.

The method of the present invention can be carried out over a wide temperature range and the limits of that range will be determined, for example, by the limit of  
15 the organic solvent used. The method can be carried out, for example, in a temperature range from about 40°C to about -30°C. Concentrations of individual reactants (e.g., chiral ligand, oxidant, etc.) can be varied as the temperature at which the method of the present invention  
20 is carried out. The saturation point (e.g., the concentration of chiral ligand at which results are maximized) is temperature-dependant. As explained previously, for example, it is possible to reduce the amount of alkaloid used when the method is carried out at lower  
25 temperatures.

The organic solvent used in the present method can be, for example, acetone, acetonitrile, THF, DME, cyclohexane, hexane, pinacolone, tert-butanol, toluene or  
30 a mixture of two or more organic solvents. These solvents are particularly suitable when NMO is the secondary oxidant.

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When potassium ferricyanide ( $K_3Fe(CN)_6$ ) is the secondary oxidant, it is advantageous to use a combination of solvents that separate into organic and aqueous phases. Although the method of the present invention can be carried out with potassium ferricyanide as the secondary oxidant using the organic solvents of the preceding paragraph, asymmetric dihydroxylation does occur but the ee's are less than when separable organic and aqueous solvent phases are employed.

The yields and ee's for a variety of organic solvents, mixed with water and a variety of substrates are shown in Tables 11-12. Table 11 shows yields and ee's for several organic solvents (with water) for a specific substrate. The ligand is either DHQD-p-chlorobenzoate (PCB) or DHQD-naphthyl ether. Table 12 shows the ee's for a variety of substrates for either t-butanol or cyclohexane as the organic phase. It is apparent from these Tables that preferred organic phase solvents include cyclohexane, hexane, ethyl ether and t-butyl methyl ether. The preferred aqueous solvent is water.

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Table 11. Solvent Study of Catalytic ADH using  
 $K_3Fe(CN)_6$

a) Solvent Effects on Styrene Diol using  
 DHQD-PCB Ligand

05 Reaction Time - 4 hours



	Solvent	Yield(%)	ee(%)
	Cyclohexane	83.5	80
	Hexane*	59.9	76
10	Iso-octane**	7	76
	t-BuOH	84.7	74
	t-Bu-O-Me	80	73
	Toluene	78	69
	Et <sub>2</sub> O	58.7	68
15	EtOAc	64.4	65
	THF	61.6	61
	Chlorobenzene	73.6	60
	CH <sub>3</sub> CN	79.0	50
	CH <sub>2</sub> Cl <sub>2</sub>	73.8	49
20	DMF	24.5	23
	MeOH	84.1	5.5

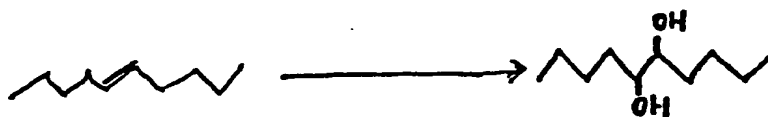
-52-

- b) Solvent Effects on Hexene Diol using  
DHQD-PCB Ligand  
Reaction Time = 24 hours



Solvent	Yield(%)	ee(%)
Cyclohexane	47	74
Hexane*	67.4	74
t-BuOH	84.5	74
t-Bu-O-Me	61.4	71
Et <sub>2</sub> O	51.1	71
EtOAc	26.7	71
Toluene	32.4	69
CH <sub>3</sub> CN	81.6	68
CH <sub>2</sub> Cl <sub>2</sub>	7.6	67
Chlorobenzene	9.3	66
THF	74.1	65

- c) Solvent Effects on Decene Diol using  
DHQD-PCB Ligand  
Reaction Time = 24 hours



Solvent	Yield(%)	ee(%)
t-BuOH	60.8	79
Cyclohexane	3.4	74
t-Bu-O-Me	7.6	71

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d) Solvent Effects on Hexene Diol using  
DHQD Naphthyl Ether Ligand  
Reaction Time - 24 hours



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15

Solvent	Yield(%)	ee(%)
t-BuOH	49.6	92
Cyclohexane	36.2	91
t-Bu-O-Me	75.4	89
Et <sub>2</sub> O	47.6	89
EtOAc	41.2	88
Toluene	24.6	87
Chlorobenzene	25.0	85
THF	78.6	83
CH <sub>3</sub> CN	90.2	81
CH <sub>2</sub> Cl <sub>2</sub>	trace	7

e) Solvent Effects on Decene Diol using  
DHQD Naphthyl Ether Ligand  
Reaction Time - 24 hours



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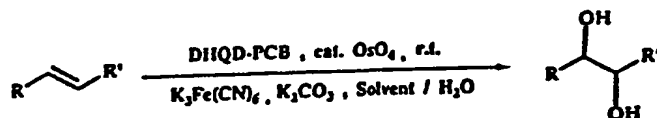
t-BuOH


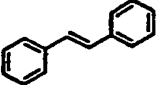
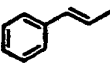
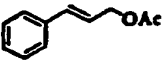
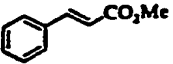


Yield(%) ee(%)  
40.7 94

- \* 5ml of t-Bu-O-Me were added to dissolve all the ligand  
\*\* 6ml of t-Bu-O-Me were added to dissolve all the ligand

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Table 12. Ee's of Various Substrates in the Catalytic ADH



	Substrate	<i>t</i> -BuOH	Cyclohexane
05		73	80
		99	99
		91	92
		91	91
		91	93
10		79	74
		74	74

In another embodiment of the present invention, styrene was combined with a chiral ligand (DHQD), acetone, water and NMO and OsO<sub>4</sub>. The plot of amine concentration vs second-order-rate-constant K for the

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catalytic cis-dihydroxylation of styrene is represented in Figure 2. The kinetic data of Figure 2 clearly shows the dramatic effect of ligand-accelerated catalysis achieved by use of the method of the present invention.

05 Point a in Figure 2 represents the rate of the catalytic process in the absence of amine ligands ( $t_{1/2} = 108$  minutes). Line b shows the rates of the process in the presence of varying amounts of quinuclidine, a ligand which substantially retards catalysis (at greater than

10 0.1M quinuclidine,  $t_{1/2}$  is greater than 30 hours). Because of the observed retarding effect of quinuclidine (ligand-decelerated catalysis) the result represented by line C was unexpected. That is, when the process occurs in the presence of dihydroquinidine benzoate derivative 1

15 (see Figure 1), the alkaloid moiety strongly accelerates the catalytic process at all concentrations (with ligand 1 = 0.4M,  $t_{1/2} = 4.5$  minutes), despite the presence of the quinuclidine moiety in its structure.

The rate of the stoichiometric reaction of styrene

20 with osmium tetroxide and that of the corresponding catalytic process were compared. The comparison indicates that both have identical rate constants

$[K_{\text{stoic}} = (5.1 \pm 0.1) \times 10^2 \text{ M}^{-1} \text{ min}^{-1} \text{ and } K_{\text{cat}} = (4.9 \pm 0.4) \times 10^2 \text{ M}^{-1} \text{ min}^{-1}]$ , and that they undergo the same rate

25 acceleration upon addition of ligand 1. Hydrolysis and reoxidation of the reduced osmium species, steps which accomplish catalyst turnover, are not kinetically significant in the catalytic process with styrene. It may be concluded that the limiting step is the same in both

30 processes and consists of the initial addition reaction forming the osmate ester (2, Figure 1). A detailed

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mechanistic study reveals that the observed rate acceleration by added ligand 1 is due to formation of an osmium tetroxide-alkaloid complex which, in the case of styrene, is 23 times more reactive than free osmium tetroxide. The rate reaches a maximal and constant value beyond an (approximate) 0.25 M concentration of ligand 1. The onset of this rate saturation corresponds to a pre-equilibrium between DHQD and osmium tetroxide with a rather weak binding constant ( $K_{eq} = 18 \pm 2 \text{ M}^{-1}$ ). Increasing the concentration of DHQD above 0.25 M does not result in corresponding increases in the enantiomeric excess of the product diol. In fact, due to the ligand-acceleration effect, the ee of the process approaches its maximum value much faster than the maximum rate is reached, which means that optimum ee can be achieved at rather low alkaloid concentrations.

At least in the case of styrene, the rate acceleration in the presence of the alkaloid is accounted for by facilitation of the initial osmylation step. The strikingly opposite effects of quinuclidine and DHQD on the catalysis can be related to the fact that although quinuclidine also accelerates the addition of osmium tetroxide to olefins, it binds too strongly to the resulting osmium(VI) ester intermediate and inhibits catalyst turnover by retarding the hydrolysis/reoxidation steps of the cycle. In contrast the alkaloid appears to achieve a balancing act which renders it near perfect for its role as an accelerator of the dihydroxylation catalysis. It binds strongly enough to accelerate addition to olefins, but not so tightly that it interferes (as does quinuclidine) with subsequent stages of the catalytic cycle. Chelating tertiary amines [e.g.,

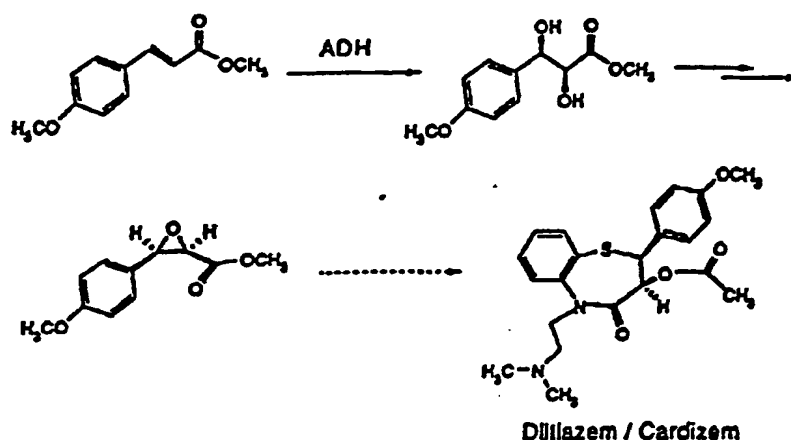
-56.1-

2,2'-bipyridine and (-)-(R,R)-N,N,N',N'-tetramethyl-1,2-cyclohexanediamine) at 0.2M completely inhibit the catalysis. Pyridine at 0.2 M has the same effect.

As represented in Table 4, the method of the present invention has been applied to a variety of olefins. In each case, the face selection rule described above has been shown to apply (with reference to the orientation of the olefin as represented in Figure 1). That is, in the case of the asymmetric dihydroxylation reaction in which the dihydroquinidine derivative is the chiral ligand, attack occurs on the re- or re,re- face) and in the case in which the dihydroquinine derivative is the chiral ligand, attack occurs on the si- or si,si- face. Thus, as demonstrated by the data presented in the Table 2, the method of the present invention is effective in bringing about catalytic asymmetric dihydroxylation; in all cases, the yield of the diol was 80-95%, and with the slow-addition modification, most olefins give ee's in the range of 40-90%.

The present method can be used to synthesize chiral intermediates which are important building blocks for biologically active chiral molecules, such as drugs. In one embodiment, the present method was used to produce an optically pure intermediate used in synthesizing the drug diltiazem (also known as cardizem). The reaction is shown in the following scheme:

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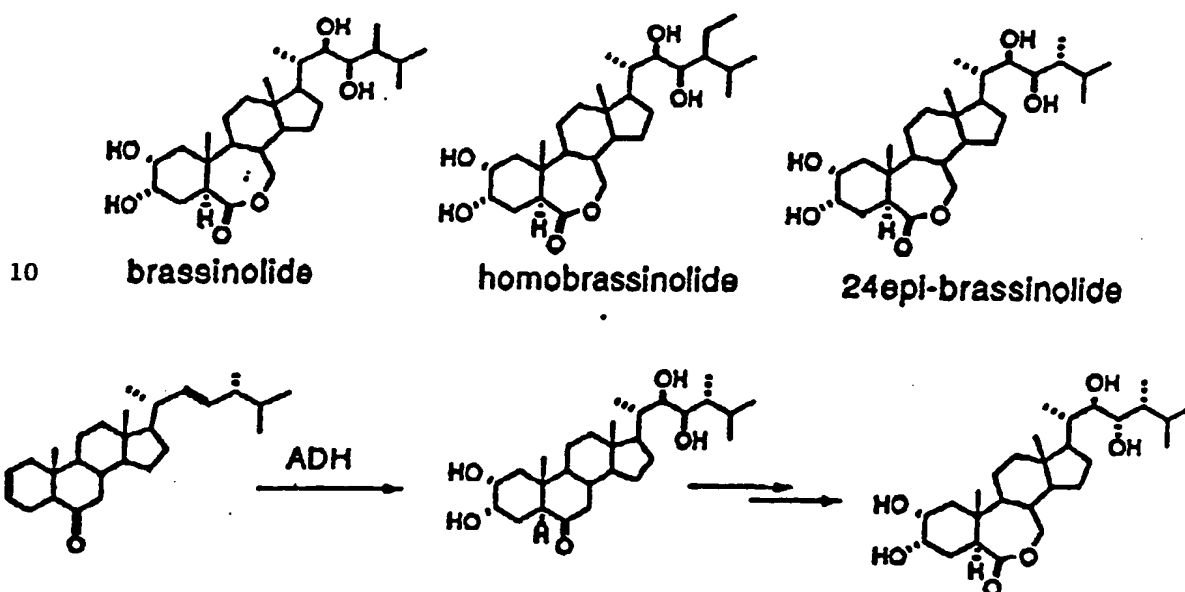


The method of the present invention is also useful to effect asymmetric vicinal oxyamination of an olefin, and may be useful for asymmetric vicinal diamination. In the case of substitution of two nitrogen or of a nitrogen and oxygen, an amino derivative is used as an amino transfer agent and as an oxidant. For example, the olefin to be modified, an organic solvent, water, a chiral ligand, an amino derivative and an osmium-containing compound are combined and the combination maintained under conditions appropriate for the reaction to occur. The amino derivative can be, for example, an N-chlorocarbamate or chloroamine T. Asymmetric catalytic oxyamination of recrystallized trans stilbene, according to the method of the present invention, is represented in Figure 2.

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In another embodiment, the present method was used to produce intermediates for the synthesis of homobrassinolide and 24-epibrassinolide, which are known to exhibit the same biological activities as brassinolide.

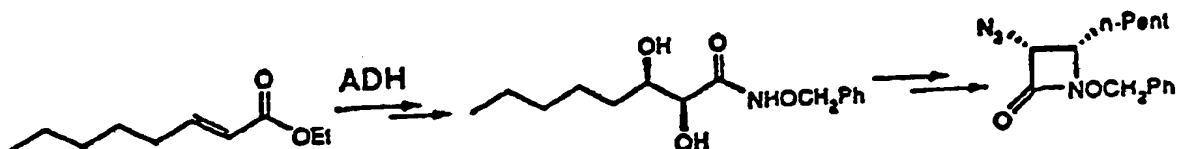
05 These brassinosteroids show very potent plant-growth activity at hormonal level and access to these compounds in a large quantity can only be achieved by synthetic means.



In another embodiment of the present method, highly optically active diol was produced from the asymmetric dihydroxylation of ethyl trans-2-octenoate. This diol

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has been converted to optically pure  $\beta$ -lactam structure, which are well-known for their antibiotic activities:



#### Example 1 Asymmetric Dihydroxylation of Stilbene

05       The following were placed sequentially in a 2L bottle (or flask): 180.2g (1.0 M) of recrystallised trans stilbene (Aldrich 96%), 62.4g (0.134 moles; 0.134 eq) of the p-chlorobenzoate of hydroquinidine (1), 450 mL of acetone, 86 mL of water (the solution is 0.261 M in

10       alkaloid 1) and 187.2 g (1.6 mol, 1.6 eq.) of solid N-Methylmorpholine N-Oxide (NMO, Aldrich 97%). The bottle was capped, shaken for 30 seconds, cooled to 0-4°C using an ice-water bath. OsO<sub>4</sub> (4.25 mL of a solution prepared using 0.120g OsO<sub>4</sub>/mL toluene; 0.002 Mol%; 0.002

15       eq.) was injected. The bottle was shaken and placed in a refrigerator at ca. 4°C with occasional shaking. A dark purple color developed and was slowly replaced by a deep orange one; the heterogeneous reaction mixture gradually became homogeneous and at the end of the reaction, a

20       clear orange solution was obtained. The reaction can be conveniently monitored by TLC (silica gel; CH<sub>2</sub>Cl<sub>2</sub>; disappearance of the starting material at a defined R<sub>f</sub>). After 17 hours, 100g of solid sodium metabisulfite (Na<sub>2</sub>S<sub>2</sub>O<sub>5</sub>) were added, the reaction mixture was shaken (1

25       minute) and left at 20°C during 15 minutes. The reaction mixture was then diluted by an equal volume of CH<sub>2</sub>Cl<sub>2</sub> and anhydrous Na<sub>2</sub>SO<sub>4</sub> added (100 g). After another 15

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minutes, the solids were removed by filtration through a pad of celite, washed three times with 250 mL portions of  $\text{CH}_2\text{Cl}_2$  and the solvent was evaporated under vacuum (rotatory-evaporator, bath temperature = 30-35°C).

05        The crude oil was dissolved in ethyl acetate (750 mL), extracted three times with 500 mL portions of 2.0 M HCl, once with 2.0 M NaOH, dried over  $\text{Na}_2\text{SO}_4$  and concentrated in vacuo to leave 190 g (89%) of the crude diol as a pale yellow solid. The enantiomeric excess of the  
10        crude R,R-diol was determined to be 78% by HPLC analysis of the derived bis-acetate (Pirkle 1A column using 5% isopropanol/hexane mixture as eluant. Retention times are:  $t_1$  = 18.9 minutes;  $t_2$  = 19.7 minutes. Recrystallization from about 1000 mL  $\text{CH}_2\text{Cl}_2$  gave 150 g (70%) of  
15        pure diol (ee = 90%). A second recrystallization gave 115g of diol (55% yield) of 99% ee. Ee (enantiomeric excess) is calculated from the relationship (for the R enantiomer, for example): percent  
e.e. =  $[(R)-(S)]/[(R)+(S)] \times 100$ .

20        The aqueous layer was cooled to 0°C and treated with 2.0M NaOH (about 500 mL) until pH = 7. Methylene chloride was added (500 mL) and the pH adjusted to 10-11 using more 2.0M NaOH (about 500 mL). The aqueous layer was separated, extracted twice with methylene chloride  
25        (2x300 mL) and the combined organic layers were dried over  $\text{Na}_2\text{SO}_4$ . The solvent was removed in vacuo to provide the alkaloid as a yellow foam. The crude alkaloid was dissolved in ether (1000 mL), cooled to 0°C (ice-bath) and treated with cry HCl until acidic pH (about 1-2).  
30        The faint yellow precipitate of p-chlorobenzoylhydroquinidine hydrochloride was collected by filtration and dried under high vacuum (0.01mm Hg).

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The free base was liberated by suspending the salt in ethyl acetate (500 mL), cooling to 0°C and adding 28% NH<sub>4</sub>OH until pH = 11 was reached. After separation, the aqueous layer was extracted twice with ethyl acetate, the  
05 combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and the solvent removed in vacuo to give the free base as a white foam.

Example 2 Asymmetric Dihydroxylation of Stilbene

To a 3 L, 3-necked, round-bottomed flask equipped  
10 with a mechanical stirrer and two glass stoppers at room temperature were added E-1,2-diphenylethene (Trans-stilbene) (180.25 g, 1.0 mol, 1.0 eq), 4-methylmorpholine N-oxide (260 mL of a 60% by wt. aqueous solution (1.5 mol, 1.5 eq) dihydroquinidine  
15 4-chlorobenzoate (23.25 g, 0.05 mol, 0.05 eq) 375 mL acetone and 7.5 mL H<sub>2</sub>O. The solution was 0.1 M in alkaloid M in olefin, and the solvent was 25% water/75% acetone (v/v). The flask was immersed in a 0°C cooling bath and stirred for 1 h. Osmium tetroxide (1.0 g, 4.0  
20 mmol.,  $4.0 \times 10^{-3}$  eq) was added in one portion producing a milky brown-yellow suspension. The reaction mixture was then stirred at 0°C for 24 h and monitored by silica TLC (3:1 CH<sub>2</sub>Cl<sub>2</sub>:Et<sub>2</sub>O v/v). At this point, sodium metabisulfite (285 g, 1.5 mol) was added, the mixture was  
25 diluted with 500 mL of CH<sub>2</sub>Cl<sub>2</sub>, warmed to room temperature, and stirred at room temperature for 1 h. Anhydrous sodium sulfate (50 g) was added and the mixture was stirred at room temperature overnight. The suspension was filtered through a 20 cm Buchner funnel,

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the filtrand was rinsed thoroughly with acetone (3 x 250 mL), and the filtrate was concentrated to a brown paste on a rotary evaporator with slight heating (bath temperature 30-40°C). The paste was dissolved in 3.5 L of EtOAc, transferred to a 6 L separatory funnel, and washed sequentially with H<sub>2</sub>O (2 x 500 mL), and brine (1 x 500 mL). The initial aqueous washes were kept separate from the subsequent acid washes which were retained for alkaloid recovery. The organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated to give the crude diol in quantitative yield (222.7 g, 1.04 mol, 104%). The ee of the crude product was determined by <sup>1</sup>H NMR analysis of the derived bis-Mosher ester to be 90%. One recrystallization from hot 95% aqueous ethanol (3 mL/g) afforded 172-180 g (80-84%) of enantiomerically pure stilbene diol as a white solid, mp 145.5-146.5°C, [α]<sub>D</sub><sup>25</sup> -91.1° (c=1.209, abs EtOH).

Example 3 Asymmetric Dihydroxylation of Stilbene

Asymmetric dihydroxylation of stilbene was carried out as described in Example 1, except that 1.2 equivalents of NMO were used.

Example 4 Asymmetric Dihydroxylation of Stilbene

Asymmetric dihydroxylation of stilbene was carried out as described in Example 1, except that 1.2 equivalents of NMO, as a 62% wt. solution in water, were used.

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Example 5 Preparation of dihydroquinidine derivativePreparation of dihydroquinidine by catalytic  
reduction of quinidine

To a solution of 16.2 g of quinidine (0.05mol) in  
05 150mL of 10%  $H_2SO_4$  (15 g conc  $H_2SO_4$  in 150mL  $H_2O$ ) was  
added 0.2 g of  $PdCl_2$  (0.022eq; 0.0011mol). The reaction  
mixture was hydrogenated in a Parr shaker at 50 psi  
pressure. After 2h, the catalyst was removed by filtra-  
tion through a pad of celite and washed with 150mL of  
10 water. The faint yellow solution so obtained was slowly  
added to a stirred aqueous NaOH solution (15 g of NaOH in  
150mL  $H_2O$ ). A white precipitate immediately formed and  
the pH of the solution was brought to 10-11 by addition  
of excess aqueous 15% NaOH. The precipitate was col-  
15 lected by filtration, pressed dry and suspended in  
ethanol (175mL). The boiling solution was quickly  
filtered and upon cooling to room temperature, white  
needles crystallized out. The crystals were collected  
and dried under vacuum ( $90^\circ C$ ; 0.05 mm Hg) overnight.  
20 This gave 8.6 g (52.7%) of pure dihydroquinidine  
mp= $169.5-170^\circ C$ . The mother liquor was placed in a  
freezer at  $-15^\circ C$  overnight. After filtration and drying  
of the crystals, another 4.2 g (21.4%) of pure material  
was obtained, raising the total amount of dihydroquini-  
25 dine to 12.8 g (74.1%).

Preparation of dihydroquinidine p-chlorobenzoate  
(ligand 1)

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From dihydroquinidine hydrochloride (Aldrich)

To a cooled (0°C) suspension of 100 g dihydroquinidine hydrochloride (0.275mol) in 300mL of dry CH<sub>2</sub>Cl<sub>2</sub> was added, over 30 minutes with efficient stirring, 115mL of Et<sub>3</sub>N (0.826eq; 3eqs) dissolved in 50mL of CH<sub>2</sub>Cl<sub>2</sub>. The dropping funnel was rinsed with an additional 20mL of CH<sub>2</sub>Cl<sub>2</sub>. After stirring 30 minutes at 0°C, 42mL of p-chlorobenzoyl chloride (0.33mol; 57.8g; 1.2eq) dissolved in 120mL of CH<sub>2</sub>Cl<sub>2</sub> was added dropwise over a period of 2h. The heterogeneous reaction mixture was then stirred 30 minutes at 0°C and 1 hour at room temperature; 700mL of a 3.0M NaOH solution was then slowly added until pH=10-11 was obtained. After partitioning, the aqueous layer was extracted with three 100mL portions of CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and the solvent removed in vacuo (rotatory evaporator). The crude oil was dissolved in 1L of ether, cooled to 0°C and treated with HCl gas until the ether solution gives a pH of about 2 using wet pH paper. The slightly yellow precipitate was collected and dried under vacuum to give 126 g (91.5%) of dihydroquinidine p-chlorobenzoate hydrochloride.

The salt was suspended in 500mL of ethyl acetate, cooled to 0°C and treated with 28% NH<sub>4</sub>OH until pH=11 was reached. After separation, the aqueous layer was extracted with two 200mL portions of ethyl acetate. The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and the solvent removed under vacuum, leaving the free base 1 as a white foam (112g; 88% overall). This material can be used without further purification, or it can be recrystallized from a minimum volume of hot acetonitrile

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to give an approximately 70-80% recovery of colorless crystals: mp: 102-104°C,  $[\alpha]^{25}_D$ -76.5° (c1.11, EtOH); IR (CH<sub>2</sub>Cl<sub>2</sub>) 2940, 2860, 1720, 1620, 1595, 1520, 1115, 1105, 1095, 1020 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) 8.72 (d, 1H, J=5Hz), 8.05 (br d, 3H, J=9.7Hz), 7.4 (m, 5H), 6.72 (d, 1H, J=7.2Hz), 3.97 (s, 3H), 3.42 (dd, 1H, J=9, 19.5Hz), 2.9-2.7 (m, 4H), 1.87 (m, 1H), 1.75 (br s, 1H), 1.6-1.45 (m, 6H), 0.92 (t, 3H, J=7Hz). Anal. Calcd for C<sub>27</sub>H<sub>29</sub>ClN<sub>2</sub>O<sub>3</sub>: C, 69.74; H, 6.28; Cl, 7.62; N, 6.02. Found: C, 69.95; H, 6.23; Cl, 7.81; N, 5.95.

#### From dihydroquinidine

To a 0°C solution of 1.22g dihydroquinidine (0.0037mol) in 30mL of CH<sub>2</sub>Cl<sub>2</sub> was added 0.78mL of Et<sub>3</sub>N (0.0056mol; 1.5eq), followed by 0.71mL of p-chlorobenzoyl chloride (0.005mol; 1.2eq) in 1mL CH<sub>2</sub>Cl<sub>2</sub>. After stirring 30 minutes at 0°C and 1 hour at room temperature, the reaction was quenched by the addition of 10% Na<sub>2</sub>CO<sub>3</sub> (20mL). After separation, the aqueous layer was extracted with three 10mL portions of CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and the solvent removed under vacuum. The crude product was purified as described above. Dihydroquinidine p-chlorobenzoate (1) was obtained in 91% yield (1.5g) as a white foam.

#### Recovery of dihydroquinidine p-chlorobenzoate

The aqueous acidic extracts (see EXAMPLE 1) were combined, cooled to 0°C and treated with 2.0M NaOH solution (500mL) until pH=7 was obtained. Methylene chloride was added (500mL) and the pH was adjusted to 10-11 using more 2.0M NaOH. The aqueous layer was

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separated and extracted with two 300mL portions of  $\text{CH}_2\text{Cl}_2$ . The combined organic layers were dried over  $\text{Na}_2\text{SO}_4$  and concentrated to leave the crude alkaloid as a yellow foam. The crude dihydroquinidine p-chlorobenzoate (1) was dissolved in 1L of ether, cooled to  $0^\circ\text{C}$  and HCl gas was bubbled into the solution until a pH of 1-2 was obtained using wet pH paper. The pale yellow precipitate of 1 as the hydrochloride salt was collected by filtration and dried under high vacuum (0.01mm Hg). The free base was liberated by suspending the salt in 500mL of ethyl acetate, cooling the heterogeneous mixture to  $0^\circ\text{C}$  and adding 28%  $\text{NH}_4\text{OH}$  (or 15%  $\text{NaOH}$ ) until pH-11 was obtained. After separation, the aqueous layer was extracted with two 100mL portions of ethyl acetate, the combined organic layers were dried over  $\text{Na}_2\text{SO}_4$  and the solvent removed in vacuo to give 56g (91% recovery) of pure dihydroquinidine p-chlorobenzoate (1) as a white foam.

Example 6 Preparation of dihydroquinine derivative

Preparation of dihydroquinine p-chlorobenzoate  
The catalytic hydrogenation and p-chlorobenzoylation were conducted as described for the dihydroquinidine p-chlorobenzoate to give a white amorphous solid in 85-90% yield. This solid can be used without further purification, or it can be recrystallized from a minimum volume of hot acetonitrile to afford colorless crystals: Mp: 130-133°C,  $[\alpha]^{25}_{\text{D}} +150^\circ$  (c 1.0, EtOH). The physical properties of the solid before recrystallization (i.e., the "white amorphous solid") are as follows:  $[\alpha]^{25}_{\text{D}}$

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D+142.1 (C-1, EtOH); IR ( $\text{CH}_2\text{Cl}_2$ ) 2940, 2860, 1720, 1620, 1595, 1508, 1115, 1105, 1095, 1020  $\text{cm}^{-1}$ ,  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  8.72 (d, 1H, J=5Hz), 8.05 (br d, 3H, J=8Hz), 7.4 (m, 5H), 6.7 (d, 1H, J=8Hz), 4.0 (s, 3H), 3.48 (dd, 1H, J=8.5, 15.8Hz), 3.19 (m, 1H), 3.08 (dd, 1H, J=11, 15Hz), 2.69 (ddd, 1H, J=5, 12, 15.8Hz), 2.4 (dt, 1H, J=2.4, 15.8Hz), 1.85-1.3 (m, 8H), 0.87 (t, 3H, J=Hz). Anal. Calcd for  $\text{C}_{27}\text{H}_{29}\text{ClN}_2\text{O}_3$ : C, 69.74; H, 6.28; Cl, 7.62; N, 6.02. Found: C, 69.85; H, 6.42; Cl, 7.82; N, 5.98.

10      Recovery of dihydroquinine p-chlorobenzoate (2)

The procedure is identical to that described above for recovery of 1.

Example 7 Procedure for Asymmetric Dihydroxylation of  
Trans-3-hexene Under "Slow Addition"  
15      Conditions

To a well stirred mixture of 0.465g (1 mmol, 0.25 eq=0.25M in L) dihydroquinidine 4-chlorobenzoate (Aldrich, 98%), 0.7g (6 mmol, 1.5 eq) N-methylmorpholine N-oxide (Aldrich, 97%), and 32 L of a 0.5M toluene solution of osmium tetroxide (16 mol,  $4 \times 10^{-3}$  equiv), 20 in 4 mL of an acetone-water mixture (10:1 v/v) at 0°C, neat 0.5 mL (0.34g, 4 mmol) trans-3-hexene (Wiley, 99.9%) was added slowly, via a gas tight syringe controlled by a syringe pump and with the tip of the syringe needle 25 immersed in the reaction mixture, over a period of 16 h. The mixture gradually changed from heterogeneous to homogeneous. After the addition was complete, the resulting clear orange solution was stirred at 0°C for an

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additional hour. Solid sodium metabisulfite ( $\text{Na}_2\text{S}_2\text{O}_5$ , 1.2g) was added and the mixture was stirred for 5 min, and then diluted with dichloromethane (8mL) and dried ( $\text{Na}_2\text{SO}_4$ ). The solids were removed by filtration, and  
05 washed three times with dichloromethane. The combined filtrates were concentrated, and the residual oil was subjected to flash column chromatography on silica gel (25g, elution with diethyl ether-dichloromethane, 2:3 v/v,  $R_f$  0.33) and collection of the appropriate fractions  
10 afforded 0.30-0.32g (85-92% yield) of the hexanediol. The enantiomeric excess of the diol was determined by GLC analysis (5% phenyl-methylsilicone, 0.25 m film, 0317 mm diameter, 29 m long) of the derived bis-Mosher ester to be 70%.

15 When the above reaction was repeated with 1.2 mL (6mmol, 1.5eq) 60% aqueous NMO (Aldrich) in 4 mL acetone, an ee of 71% was obtained. Thus, this aqueous NMO gives equivalent results and is almost twenty times less expensive than the 97% solid grade. With an alkaloid  
20 concentration of only 0.1M (i.e., 0.186g) and with an olefin addition period of 20 hours at 0°C, the ee was 65%. A small sacrifice in ee thus leads to a large saving in alkaloid. At 0°C, both trans-3-hexene and trans- -methylstyrene reach their maximum ee value  
25 between 0.20 and 0.25M alkaloid concentration.

Example 8 Asymmetric Dihydroxylation of  
1-Phenylcyclohexene with  $\text{Et}_4\text{NOAc} \cdot 4\text{H}_2\text{O}$

The procedure set out in Example 1 was followed, except that 1-phenylcyclohexene (1.0M) was substituted

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for trans-stilbene. The reaction was allowed to proceed for three days, after which only 40% conversion to the diol was obtained (8% ee).

The above procedure was repeated, with the difference that 2 equivalents of tetraethyl ammonium acetate ( $\text{Et}_4\text{NOAc} \cdot 4\text{H}_2\text{O}$ ) was added to the reaction mixture at the beginning of the reaction. Fifty-two (52%) percent ee was obtained using this procedure, and the reaction was finished in about one day.

10 Example 9 Asymmetric Dihydroxylation of trans-Stilbene  
under "phase-transfer" conditions in toluene

To a well-stirred mixture of 58.2 mg (0.125 mmol; 0.25 eq.) of the p-chlorobenzoate of hydroquinidine, 1 mL of toluene, 88 mg (0.75 mmol; 1.5 eq.) of N-methyl-morpholine N-oxide, 181 mg (1 mmol; 2 eq.) of tetra-methylammonium hydroxide pentahydrate, 57  $\mu\text{L}$  (2 mmol; 2 eq.) of acetic acid, 0.1 mL of water, and  $\text{OsO}_4$  (4.2  $\mu\text{L}$  of solution prepared using 121 mg  $\text{OsO}_4/\text{mL}$  toluene; 0.004 Mol%, 0.004 eq.) at room temperature, a toluene solution (1 mL) of 90 mg (0.4 mmol) of trans-stilbene was added slowly, with a gas-tight syringe controlled by a syringe pump and with the tip of the syringe needle immersed in the reaction mixture, over a period of 24 h. After the addition was completed, 10%  $\text{NaHSO}_3$  solution (2.5 mL) was added to the mixture, and the resulting mixture was stirred for 1 h. Organic materials were extracted with ethyl acetate, and the combined extracts were washed with brine and dried over  $\text{Na}_2\text{SO}_4$ . The solvent was evaporated under reduced pressure, and the residual oil was subjected to column chromatography on silica gel (5 g,

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elution with hexane-ethyl acetate, 2:1 v/v,  $R_f$  0.17) to afford 67.3 mg (63%) of the diol. The enantiomeric excess of the diol was determined by HPLC analysis of the derived bis-acetate (Pirkle 1A column using 5% isopropanol/hexane mixture as eluant. Retention times are:  $t_1$  = 22.6 minutes;  $t_2$  = 23.4 minutes) to be 94%.

Example 10 Asymmetric Dihydroxylation of trans-Methyl 4-methoxycinnamate under phase-transfer conditions in toluene

To a well-stirred mixture of 116.3 mg (0.25 eq.) of the p-chlorobenzoate of hydroquinidine, 2 mL of toluene, 175.8 mg (1.5 mmol; 1.5 eq.) of N-methylmorpholine N-oxide, 522 mg (2 mmol; 2 eq.) of tetraethylammonium acetate tetrahydrate, 0.2 mL of water, and  $\text{OsO}_4$  (8.4  $\mu\text{L}$  of solution prepared using 121 mg  $\text{OsO}_4/\text{mL}$  toluene; 0.004 Mol%, 0.004 eq.) at room temperature, a toluene solution (1 mL) of 192 mg (1 mmol) of trans-methyl 4-methoxycinnamate was added slowly, with a gas-tight syringe controlled by a syringe pump and with the tip of the syringe needle immersed in the reaction mixture, over a period of 24 h. After the addition was complete, 10%  $\text{NaHSO}_3$  solution (5 mL) was added to the mixture, and the resulting mixture was stirred for 1 h. Organic materials were extracted with ethyl acetate, and the combined extracts were washed with brine and dried over  $\text{Na}_2\text{SO}_4$ . The solvent was evaporated under reduced pressure, and the residual oil was subjected to column chromatography on silica gel (10 g, elution with hexane-ethyl acetate, 2:1 v/v  $R_f$  0.09) to afford 118.8 mg (53%) of the diol. The enantiomeric excess of the diol was determined by

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HPLC analysis of the derived bis-acetate (Pirkle Covalent Phenyl Glycine column using 10% isopropanol/hexane mixture as eluant. Retention times are:  $t_1$  = 25.9 minutes;  $t_2$  = 26.7 minutes) to be 84%.

05 Example 11 Asymmetric Dihydroxylation of trans-Stilbene  
in the presence of Boric Acid

To a well-stirred mixture of 58.2 mg (0.125 mmol; 0.25 eq) of the p-chlorobenzoate of hydroquinidine, 70 mg (0.6 mmol; 1.2 eq.) of N-methylmorpholine N-oxide, 37 mg  
10 (0.6 mmol; 1.2 eq.) of boric acid, 0.5 mL of dichloromethane, and  $\text{OsO}_4$  (4.2  $\mu\text{L}$  of a solution prepared using 121 mg  $\text{OsO}_4/\text{mL}$  toluene; 0.004 Mol%, 0.004 eq.) at room temperature, a dichloromethane solution (1 mL) of 90 mg  
15 (0.5 mmol) of trans-stilbene was added slowly, with a gas-tight syringe controlled by a syringe pump and with the tip of the syringe needle immersed in the reaction mixture, over a period of 24 h. After the addition was complete, 10%  $\text{NaHSO}_3$  solution (2.5 mL) was added to the mixture, and the resulting mixture was stirred for 1 h.  
20 Organic materials were extracted with ethyl acetate, and the combined extracts were washed with brine and dried over  $\text{Na}_2\text{SO}_4$ . The solvent was evaporated under reduced pressure, and the residual oil was subjected to column chromatography on silica gel (5 g, elution with hexane-ethyl acetate, 2:1 v/v,  $R_f$  0.17) to afford 78.3 mg (73%)  
25 of the diol. The enantiomeric excess of the diol was determined by  $^1\text{H}$ -NMR (solvent:  $\text{CDCl}_3$ ) analysis of the derived bis-Mosher ester to be 94%.

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Example 12 Asymmetric Dihydroxylation of trans-Methyl  
4-methoxycinnamate in the presence of Boric  
Acid

To a well-stirred mixture of 116.3 mg (0.25 mmol;  
05 0.25 eq.) of the p-chlorobenzoate of hydroquinidine,  
175.8 mg (1.5 mmol; 1.5 eq.) of N-methylmorpholine  
N-oxide, 74.4 mg (1.2 mmol; 1.2 eq.) of boric acid, 1 mL  
of dichloromethane, and  $\text{OsO}_4$  (8.4  $\mu\text{L}$  of a solution  
prepared using 121 mg  $\text{OsO}_4/\text{mL}$  toluene, 0.004 mol%, 0.004  
10 eq.) at room temperature, a dichloromethane solution  
(1mL) of 192 mg (1 mmol) of trans-methyl 4-  
methoxycinnamate was added slowly, with a gas-tight  
syringe controlled by a syringe pump and with the tip of  
the syringe needle immersed in the reaction mixture, over  
15 a period of 24 h. After the addition was complete, 10%  
 $\text{NaHSO}_3$  solution (5 mL) was added to the mixture, and the  
resulting mixture was stirred for 1 h. Organic materials  
were extracted with ethyl acetate, and the combined  
extracts were washed with brine and dried over  $\text{Na}_2\text{SO}_4$ .  
20 The solvent was evaporated under reduced pressure, and  
the residual oil was subjected to column chromatography  
on silica gel (10 g, elution with hexane-ethyl acetate,  
2:1 v/v,  $R_f$  0.09) to afford 151.1 mg (67%) of the diol.  
The enantiomeric excess of the diol was determined by  
25 HPLC analysis of the derived bis-acetate (Pirkle Covalent  
Phenyl Glycine column using 10% isopropanol/hexane  
mixture as eluant. Retention times are:  $t_1$  = 24.0  
minutes;  $t_2$  = 24.7 minutes) to be 76%.

Example 13 Asymmetric Dihydroxylation of trans- $\beta$ -  
Methylstyrene in the presence of Boric Acid

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To a well-stirred mixture of 58.2 mg (0.125 mmol; 0.25 eq) of the p-chlorobenzoate of hydroquinidine, 70 mg (0.6 mmol; 1.2 eq) of N-methylmorpholine N-oxide, 72 mg (0.6 mmol; 1.2 eq) of phenylboric acid, 0.5 mL of  
05 dichloromethane, and  $\text{OsO}_4$  (4.2  $\mu\text{L}$  [of a solution prepared using 121 mg  $\text{OsO}_4$ /mL toluene; 0.004 Mol%, 0.004 eq) at  $0^\circ\text{C}$ , a dichloromethane solution] (0.5 mL), 65  $\mu\text{L}$  (0.5 mmol) trans- $\beta$ -methylstyrene was added slowly, with a gas-tight syringe controlled by a syringe pump and with  
10 the tip of the syringe needle immersed in the reaction mixture, over a period of 24 h. After the addition was complete, 10%  $\text{NaHSO}_3$  solution (2.5 mL) was added to the mixture, and the resulting mixture was stirred for 1 h. Organic materials were extracted with ethyl acetate, and  
15 the combined extracts were washed with brine and dried over  $\text{Na}_2\text{SO}_4$ . The solvent was evaporated under reduced pressure, and the residual oil was subjected to column chromatography on silica gel (5 g, elution with hexane-ethyl acetate, 2:1 v/v,  $R_f$  0.62) to afford 109 mg (91%)  
20 of the phenylborate. The phenylborate was dissolved into acetone (3 mL) and 1,3-propanediol (0.5 mL), and the resulting mixture was stood for 2 h at room temperature. The solvent was evaporated under reduced pressure, and the residual oil was subjected to column chromatography on  
25 silica gel (5g, elution with hexaneethyl acetate, 2:1 v/v,  $R_f$  0.10) to afford 48.6 mg (70%) of the diol. The enantiomeric excess of the diol was determined by HPLC analysis of the derived bis-acetate (Pirkle 1A column using 0.5% isopropanol/hexane mixture as eluant.  
30 Retention times are:  $t_1$  = 17.1 minutes;  $t_2$  = 18.1 minutes) to be 73%.

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Example 14 General Method for the Asymmetric  
Dihydroxylation of trans-Stilbene Using A  
Polymeric Alkaloid Ligand

To a magnetically stirred suspension of the alkaloid  
05 copolymer (such as polymers 2-4, Table 1; 0.25 eq based  
on alkaloid incorporated), NMO (1.5 eq), and tetraethyl-  
ammonium acetate tetrahydrate (1.0 eq) in acetone-water  
(10/1, v/v) a solution of  $\text{OsO}_4$  (0.01 eq) in either  
toluene or acetonitrile was added. After stirring for  
10 10-30 minutes, trans-stilbene (1.0 eq) was added and the  
reaction mixture was stirred for the given time and  
monitored by silica gel TLC (hexane-EtOAc 2/1, v/v). The  
concentration of olefin in the reaction mixture was  
0.3-0.4 M. After the reaction was complete, the mixture  
15 was diluted with acetone, water, hexane or ether and  
centrifuged or filtered to separate the polymer from the  
reaction mixture. The supernatant was then worked up as  
described by Jacobsen et al., J. Am. Chem. Soc., 110:1968  
(1988).

20 Example 15 Asymmetric Dihydroxylation of trans-Stilbene  
Using A Polymer-Bound Alkaloid Ligand and  
Potassium Ferricyanide

To a well-stirred mixture of the alkaloid polymer  
(0.05 mmol, based on alkaloid incorporated), potassium  
25 ferricyanide (0.198 g, 0.6 mmol) and potassium carbonate  
(0.83 g, 0.6 mmol) in tert-butanol (1.5 mL) and water  
(1.5 mL), was added  $\text{OsO}_4$  solution (0.0025 mmol) in  
acetonitrile. After stirring for 10 min, trans-stilbene  
(36 mg, 0.2 mmol) was added and the mixture was stirred  
30 for the given time and monitored by silica gel TLC. When

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the reaction was complete, water (3.0 mL) was added and the mixture was filtered. The filtrate was extracted with dichloromethane (5 mL x 2). the organic layer was stirred for 1 h with excess sodium metabisulfite and sodium sulfate. This suspension was filtered and the filtrate was concentrated to provide crude diol, which was purified on a silica gel column.

Example 16 Asymmetric Dihydroxylation of Olefins  
in the Presence of Potassium Ferricyanide

The general procedure for asymmetric dihydroxylation of olefins using potassium ferricyanide:

To a well-stirred mixture of 0.465 g (1 mmol, 0.5 equiv - 0.033 M in ligand) dihydroquinidine p-cholorobenzoate (Aldrich, 98%), 1.980 g (6 mmol, 3.0 equiv) potassium ferricyanide, 0.830g (6 mmol, 3.0 equiv) potassium carbonate, and 0.5 mL of a 0.05 M tert-butyl alcohol solution of osmium tetroxide (0.025 mmol, 0.0125 equiv) in 30 mL of a tert-butyl alcohol-water mixture (1:1, v/v) at room temperature, olefin (2 mmol) was added at at once. The reaction mixture was stirred for 24 h at room temperature. Solid sodium sulfite ( $\text{Na}_2\text{SO}_3$ , 1.5g) was added, and the mixture was stirred for an additional hour. The solution obtained was concentrated to dryness under reduced pressure, and the residue was extracted with three portions of ether. The combined extracts were dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated. The residue was purified by column chromatography (silica gel, dichloromethane-ether).

Example 17 Preparation of 9-O-Phenyldihydroquinidine

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To a suspension of dihydroquinidine (4.0 g) in THF (40 mL) was added  $\eta$ -BuLi (2.5 M solution in hexane, 4.95 mL) at 0°C. The ice bath was removed and the reaction mixture stood at room temperature for 10 minutes. To the  
05 resulting yellow solution, solid cuprous chloride (1.2 g) was added. After stirring for 30 minutes, pyridine (30 mL) and HMPA (1 mL) were added. After stirring for 5 minutes, phenyl iodide (1.37 mL) was added and the mixture was stirred at reflux for 36h. To the resulting  
10 mixture, aqNH<sub>4</sub>OH was added and the mixture was extracted with ethyl ether. The extract was dried over MgSO<sub>4</sub>. The solvent was evaporated under reduced pressure, and the residue was subjected to column chromatography on silica gel (100 g, elution with ethyl acetate-ethanol, 9:1 v/v,  
15 Rf 0.23) to afford 1.77 g(y. 36%) of 9-O-phenyldihydroquinidine.  
<sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  8/68 (1H, d, J = 4.5 Hz), 8.08 (1H, d, J = 9 Hz), 7.3-7.5 (3H, m), 7.17 (2H, t, J = 8 Hz), 6.89 (1H, t, J = 8 Hz), 6.78 (2H, d, J = 8 Hz), 6.02 (1H, d, J = 3 Hz),  
20 4.00 (3H, s), 2.7-3.3 (5H, m), 2.2-2.4 (1H, m), 1.4-1.9 (6H, m), 1.1-1.3 (1H, m), 0.97 (3H, t, J = 7 Hz).

Example 18 Asymmetric Dihydroxylation of Trans-3-Hexene Using 9-O-Phenyldihydroquinidine and Potassium Ferricyanide

25 To a well-stirred mixture of 46 mg of 9-O-phenyldihydroquinidine, 396 mg of potassium ferricyanide, 166 mg of potassium carbonate and 8  $\mu$ L of a 0.63 M toluene solution of osmium tetroxide in 6 mL of t-butyl alcohol-water (1:1, v/v) at room temperature was added 50  $\mu$ L of  
30 trans-3-hexene all at once. The reaction mixture was

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stirred for 20 h at room temperature. Solid sodium sulfite was added and the mixture was stirred for 3 h. The solid was removed by filtration and the filtrate was extracted with ethyl ether. The extract was dried over 05  $\text{MgSO}_4$ . The solvent was evaporated under reduced pressure, and the residue was subjected to column chromatography on silica gel (elution with hexane-ethyl acetate, 2:1 v/v) to afford 40.5 mg (y. 85%) of the diol. The enantiomeric excess of the diol was determined by GLC 10 analysis of the derived bis-Mosher ester to be 83% (5% phenyl-methylsilicone, 0.25 m film, 0.317 mm diameter, 29 m long. Retention times are  $t_1 = 15.6$  min;  $t_2 = 16.0$  min.).

15 Example 19 Asymmetric Oxyamination of Trans-Stilbene  
Using N-Chloro-N-Sodio-t-Butylcarbamate

To a well-stirred mixture of 81 mg trans-stilbene, 122 mg of N-chloro-N-sodio-t-butylcarbamate, 95 mg of mercuric chloride, 209 mg of dihydroquinidine p- 20 chlorobenzoate and 370  $\mu\text{L}$  of water acetonitrile (5 mL) was added 9  $\mu\text{L}$  of a 0.5 M toluene solution of osmium tetroxide. The mixture was stirred at room temperature overnight. Solid sodium sulfite and water were added, and the mixture was stirred at 60°C for 1 hour. The 25 mixture was extracted with dichloromethane and the extract was dried over  $\text{MgSO}_4$ . The solvent was evaporated under reduced pressure, and the residue was subjected to column chromatography on silica gel (elution with hexane-ethyl acetate, 4:1 v/v, Rf 0.13) to afford 131 mg (y. 30 93%) of the aminoalcohol. The enantiomeric excess of the

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aminoalcohol was determined by HPLC analysis (Pirkle Covalent Phenyl Glycine column using 10% isopropanol/hexane mixture as eluant. Retention times are:  $t_1$  = 12.7 min;  $t_2$  = 15.2 min.) to be 65%.

- 05  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.1-7.4 (10H, m), 5.3-5.4 (1H, m), 4.95 (1H, d,  $J$  = 3.5 Hz), 4.8-5.0 (1H, m), 2.6-2.7 (1H, m), 1.34 (9H, ).

Example 20 Asymmetric Dihydroxylation Using Heterocyclic Chiral Ligands

10 Ligand preparations and properties

- 1a: To a room temperature suspension of DHQD (48.9 g, 0.15 mol) in dry DMSO (600 ml) are added NaH (4.0 g, 0.17 mmol) followed by pyridine (12.1 ml, 0.15 mol), CuI (28.6 g, 0.15 mol), and then 9-phenanthryl iodide (45.6 g, 0.15 mol) under argon. After 70 h of reaction at 120°C, 1a is obtained in 73% yield (55.0 g). See also: Lindley, J. Tetrahedron, 1984, 40, 1433 and references therein.

- 20 m.p. 98-100°C,  $^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.7 (m, 2), 8.38 (d, 1), 8.07 (d, 1), 7.75 (m, 2), 7.57 (d, 1), 7.4 (m, 6), 6.63 (s, 1), 6.63 (d, 1), 4.03 (s, 3), 3.38 (m, 1), 3.16 (m, 1), 2.97 (m, 2), 2.78 (m, 1), 2.55 (s, br., 1), 2.39 (t, 1), 1.81 (s, 1), 1.6 (m, 6), 0.98 (t, 3).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 158.2, 150.4, 147.5, 144.6, 143.7, 25 132.3, 132.0, 131.5, 127.4, 127.2, 126.7, 126.6, 126.4, 124.5, 122.8, 122.2, 121.9, 118.1, 104.8, 100.9, 78.8, 60.3, 55.8, 51.0, 50.1, 37.4, 27.1, 26.6, 25.2, 21.7, 11.8. IR (KBr):  $\nu$  = 1622, 1508, 1452 and 1227  $\text{cm}^{-1}$ .  $[\alpha]_D^{23}$  = -281.3 ( $\text{CHCl}_3$ ,  $c$  = 1.12  $\text{g ml}^{-1}$ ).

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1b: To a room temperature suspension of DHQD (65.2 g, 0.20 mol) in DMF (300 ml) are added NaH (6.06 g, 0.24 mol), followed by 2-chloro-4-methylquinoline (42.6 g, 0.24 mol). After stirring for 24 h at room temperature, 2a is obtained in 82% yield (76.3 g). m.p. 151-153°C.  $^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 0.93 (3H,t,J = 7.2Hz), 1.4-1.7 (6H,m), 1.76 (1H,s), 2.12 (1H,t,J = 10.0Hz), 2.61 (3H,s), 2.7-3.0 (4H,m), 3.43 (1H,dd,J = 6.4,8.8Hz), 3.94 (3H,s), 6.82 (1H,s), 7.2-7.6 (6H,m), 7.73 (1H,d,J = 2.5Hz), 7.81 (1H,d,J = 8.0Hz), 7.98 (1H,d,J = 9.2Hz), 8.67 (1H,d,J = 4.6Hz).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  = 11.8, 18.4, 22.9, 25.2, 25.8, 27.1, 37.2, 49.8, 50.6, 55.4, 59.2, 73.1, 101.7, 112.5, 118.5, 121.4, 123.3, 123.7, 125.2, 127.5, 129.0, 131.3, 144.5, 145.8, 147.3, 157.4, 160.4. IR(KBr): 1608, 1573, 1508, 1466, 1228, 1182, 1039, 848, 758  $\text{cm}^{-1}$ .  $[\alpha]_D^{21}$  = -194.7° (EtOH, c = 1.0). 2a and 2b can be synthesized in a similar fashion. Like the p-chlorobenzoate derivatives, these two new types of ligands are now available from Aldrich.

20 Typical Procedure for the Catalytic ADH (vinlycyclooctane)

To a well-stirred mixture of DHQD-PHN 1a (100mg, 0.2 mmol, 0.02 equiv.),  $\text{K}_3\text{Fe}(\text{CN})_6$  (9.88 g, 30 mmol, 3 equiv.), and  $\text{K}_2\text{CO}_3$  (4.15 g, 30 mmol, 3 equiv.) in a tert-BuOH- $\text{H}_2\text{O}$  mixture (100 ml, 1/1, v/v) was added potassium osmate (VI) dihydrate (7.4 mg, 0.02 mmol, 0.002 equiv.). The resulting yellow solution was cooled to 0°C and vinylcyclooctane (1.65 ml, 10 mmol) was added. The reaction mixture was stirred for 18 h at 0°C.  $\text{Na}_2\text{SO}_3$  (7.5 g) was added and the resulting mixture was stirred for 30 minutes. The two phases were separated and the

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aqueous phase was then extracted with  $\text{CH}_2\text{Cl}_2$ . The combined organic solution was evaporated and the residue was diluted with ethyl acetate, washed with 1 M  $\text{H}_2\text{SO}_4$ , aqueous  $\text{NaHCO}_3$ , and brine, and dried. Concentration and  
05 flash chromatography afforded 1.63 g (95%) of cyclooctylethanediol as a colorless oil;  $[\alpha]_D^{22} -4.1^\circ$  (EtOH,  $c=1.0$ ). The ee of the diol was determined by HPLC analysis of the derived bis-MTPA ester to be 93%. The alkaloid ligand was recovered in 82% yield by adjusting  
10 the acidic aqueous washes to pH 11 with  $\text{Na}_2\text{CO}_3$ , extracting with  $\text{CH}_2\text{Cl}_2$ .

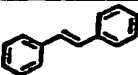





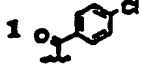

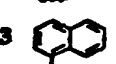
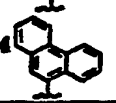
Example 21 Asymmetric Dihydroxylation of Olefins Using  
9-O-phenanthryl and 9-O-naphthyl  
dihydroquinidine Ligands

15 This example describes the enantioselectivity-ligand structure relationship of the 9-O-aryl DHQD ligands which explains the advantages of these new ligands.

The enantiometric excesses obtained in the catalytic ADH reactions of various olefins using 9-O-aryl DHQD are  
20 summarized in Table 13. These 9-O-aryl DHQD ligands can be easily prepared in one step from commercially available hydroquinidine, NaH, CuI, and the corresponding aryl halide in moderate to good yields (52-70%), as describe below. Compared to DHQD  $p$ -chlorobenzoate 1,

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Table 13: Catalytic Asymmetric Dihydroxylation of Olefins<sup>a</sup>

		ee, <sup>b</sup> %					
olefin:							
05	1 	99	91	91	79	74	67
	2 	94	89	91	88	83	88
	3 	99	91	96	94	92	94
	4 	99	93	98	96	92	94

<sup>a</sup>All reactions were carried out as described by Kwong, H.-L., et al., *Tetrahedron Lett.*, 30:2041 (1989), except that 25 mol% of ligand was used. Reactions were performed at room temperature. In all cases the isolated yield of the diol was 75-95%. <sup>b</sup>The enantiomeric excesses were measured by conversion of the diol into the corresponding bisesters of (R)-(+)- $\alpha$ -methoxytrifluoromethylphenylacetic acid and determination of the ratio of diastereomers by GLC, HPLC, and/or <sup>1</sup>H NMR.

9-O-phenyl DHQD 2 is obviously a better ligand for aliphatic olefins, but not for aromatic olefins. By contrast, 9-O-naphthyl 3 and especially, 9-O-phenanthryl DHQD 4 exhibit much higher enantioselectivities for both aromatic and aliphatic olefins.

In order to obtain information regarding the relationship between ligand structure and enantioselectivity in the ADH, various 9-O-substituted DHQD derivatives were next examined. The structures of

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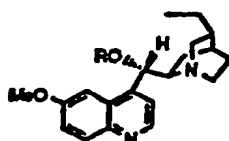
the 9-O-substituents of these DHQD derivatives and their enantioselectivities for the typical aliphatic and aromatic olefins, trans-5-decene and trans-stilbene are shown in Table 14. Each structure in Table 14 is drawn with its expected spatial orientation in the reaction intermediate, osmate ester such that the more sterically hindering 6-methoxyquinoline moiety is on the left side of the structure<sup>11</sup>.

In Group A, those derivatives having a second benzene ring on the right side (1,3 and 4) all give higher ee's for stilbene (99%) than the one (2) without that second benzene ring (94%). In addition, the naphthyl derivative (3) gives higher ee for decene (94%) than does the phenyl derivative (2) (88%). These two results suggest that the benzene ring on the right side is important for high enantioselectivities with both aliphatic and aromatic olefins. On the other hand, the fact that derivatives (2-4) give much higher ee's for decene (88-96%) than does the *p*-chlorobenzoate derivative (1) (79%) shows the importance of the aromatic ring on the left side for aliphatic olefins.

Next, the *o*-position of the phenyl derivatives was examined (2, 5-7, Group B). While the phenyl-derivative (2) and the 2-methylphenyl derivative (6) give fairly high ee's for decene (88, 91%), the 2-pyridyl (5) and the 2,6-dimethylphenyl (7) derivatives do not produce satisfactory enantioselectivities (71, 50%). This indicates that the left *o*-position of the phenyl derivative needs to be just C-H for high enantioselectivity. The effect at *m*- and *p*-positions can be understood by comparing the derivatives in Group C and D. These results indicate that both the *m*- and *p*-positions need to be C-H or larger for high ee's with aliphatic olefins.

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Table 14



	decene (ee %)	R	stilbene (ee %)		decene (ee %)	R	stilbene (ee %)		decene (ee %)	R	stilbene (ee %)		decene (ee %)	R	stilbene (ee %)
05 1	79		99	2	88		94	3	94		99	11	93		97
2	88		94	5	71		96	8	95		98	12	80		94
3	94		99	6	91		95	9	87		96				
4	96		99	7	50		Not Tested	10	92		96				
Group A				Group B				Group C				Group D			

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Procedure for the Synthesis of 9-O-aryl DHQD (3) and (4)

Into a 100 ml 3-necked round-bottomed flask 2.00g  
(6.12 mmol) of dihydroquinidine (Note: All addition of  
reagents and reaction were done under argon) and 0.160g  
05 (6.73 mmol) of NaH were dissolved in 20ml of  
dimethylsulfoxide. After stirring for about 10 minutes  
the reaction mixture became a clear orange-yellow  
solution. At this point, 1.17g (6.12 mmol) of copper(I)  
iodide and 0.50 ml (6.12 mmol) of pyridine and 6.12 mmol  
10 of 1-naphthyl iodide or phenanthryl bromide,  
respectively, were added and the reaction mixture was

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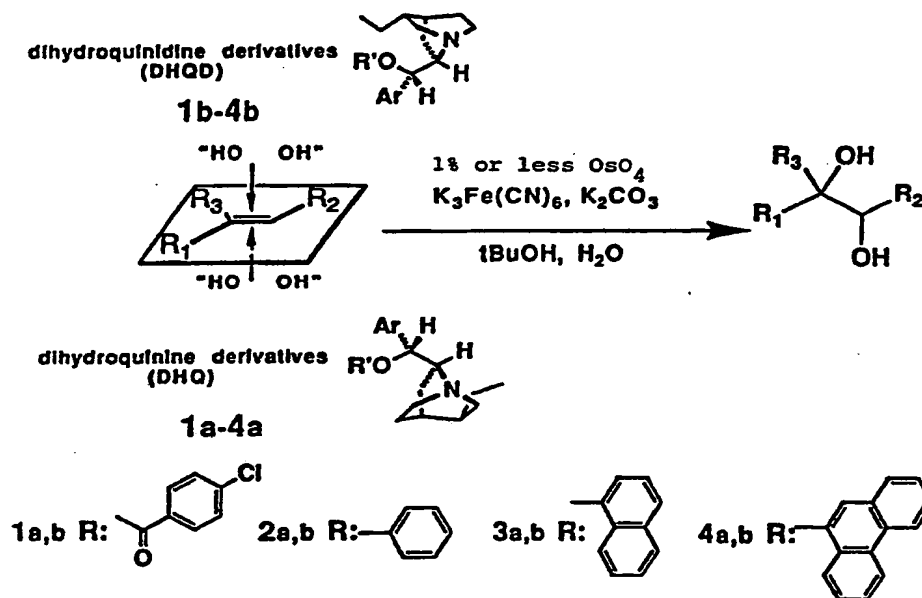
- heated for 3 days at 120°C. Then the reaction mixture was allowed to cool down to room temperature and dichloromethane (30 ml) and water (30 ml) were added. Next, 10 ml of concentrated ammonium hydroxide was slowly added to the reaction mixture. After stirring for 15 minutes the two phases were separated. The aqueous phase was extracted two times with dichloromethane (20 ml). The organic phases were combined, washed three times with water (10 ml), and evaporated. The resulting residue was then purified by column chromatography (silica gel, using 5% methanol/ethyl acetate as the eluting solvent), yielding slightly yellow crystals of 9-O-naphthyl DHQD (3) (yield: 70%) or 9-O-phenanthryl DHQD (4) (yield: 52%) respectively.
- (3): m.p. 75-77°C.  $^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 8.60 (dd,2), 8.05 (dd,1), 7.80 (d,1), 7.4 (m,5), 7.07 (t,1), 6.42 (d,1), 6.24 (d,1), 3.99 (s,3), 3.31 (dt,1), 3.17 (dd,1), 2.92 (dd,2), 2.78 (m,1), 2.37 (m,2), 1.79 (s,br., 1), 1.6 (m,6), 0.96 (t,3).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 158.2, 150.4, 147.5, 132.3, 132.0, 131.5, 127.4, 127.2, 126.7, 126.6, 126.4, 124.5, 122.8, 122.2, 121.9, 118.1, 104.8, 100.9, 78.8, 60.3, 55.8, 51.0, 50.1, 37.4, 27.1, 26.6, 25.2, 21.7, 11.8, IR (KBr):  $\nu$  = 1622, 1508, 1452 and 1227  $\text{cm}^{-1}$ .  $[\alpha]_{\text{D}}^{23}$  = -281.3 ( $\text{CHCl}_3$ ,  $c$  = 1.12g  $\text{ml}^{-1}$ )
- The 9-O-aryl DHQD (3) and (4) were prepared according to the Ullmann phenyl ether synthesis: Lindley, J., Tetrahedron, 40:1433 (1984) and references therein.
- All these 9-O-substituted DHQD derivatives (5), (9) and (10) were synthesized at room temperature without copper(I) iodide.

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Example 22 Asymmetric Dihydroxylation of Olefins Using Dihydroquinine Arylethers

A high level of asymmetric induction was achieved in the asymmetric dihydroxylation of a wide variety of  
 05 olefins using 9-O-aryldihydroquinines as ligands. (B. Lohray, et al., Tetrahedron Lett., 30:2041 (1989))

The asymmetric dihydroxylation using catalytic amounts of osmium tetroxide and cinchona alkaloid derivatives is one of the few examples of reactions  
 10 combining high levels of enantioselectivity for a large range of substrates, good to excellent yields, simple and mild experimental conditions. Another point worth emphasizing, is the availability of the requisite cinchona alkaloids. Both enantiomers of the diol can  
 15 be obtained choosing dihydroquinine (DHQ) or dihydroquinidine (DHQD) derivatives):



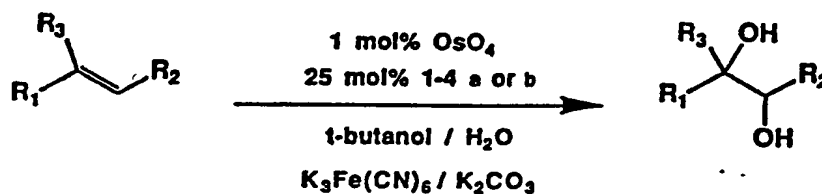
- 87 -

Recent advances in our group using potassium ferricyanide as stoichiometric oxidant and new aryl and heteroaromatic derivatives of the dihydroquinidine and dihydroquininine have made it possible to obtain good to  
05 excellent yields and enantioselectivities for many different kinds of substrates. (H-L. Kwong, et al., Tetrahedron Lett., 31:2999; M. Minato, et al., J. Org. Chem., 55:766 (1990); T. Shibata, et al., Tetrahedron Lett., 31:3817 (1990); In this example we report details  
10 about the 9-O-aryldihydroquinines 2a-4a.

The trend for the dihydroquinine and dihydroquinidine derivatives are very similar (see Table 15). As in the dihydroquinidine series, the DHQ phenanthryl ether derivative 4a is greatly superior to 1a  
15 for a wide range of substrates. The improvement is especially dramatic for transdisubstituted aliphatic olefins such as 5-decene (entry 1) as well as for terminal saturated olefins (entries 6 and 7) and for alkyl substituted  $\alpha,\beta$  unsaturated carbonyl compounds  
20 (entry 3). The changes observed in case of aromatic olefins (entries 4 and 5) were slight.

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Table 15



entry	olefin	ee using 1a (ee using 1b)	ee using 2a (ee using 2b)	ee using 3a (ee using 3b)	ee using 4a (ee using 4b)
1		70% (79%)	75% (88%)	86% (94%)	91% (96%) [93%] 0°C
05 2		67% (74%)	75% (83%)	82% (92%)	85% (94%)
3		64%	70%	83%	91% [94%] 0°C
4		97% (99%)	93% (94%)	94% (99%)	96% (99%)
5		66% (74%)	57% (61%)	62% (72%)	69% (73%)
6	1-decene	41% (45%)	44%	56% (66%)	63%
10 7		54% (64%)	58%	73% (84%)	83% (88%) [88% (93%)] 0°C

All but the three indicated reactions were carried out at room temperature. In all cases the isolated yield was 70-95%. Enantiomeric excesses were determined by GC or HPLC analysis of the derived bis-Mosher esters.

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Unlike the difference observed using the dihydroquinidine derivatives, the gap in enantioselectivities between naphthyl-DHQ and phenanthryl-DHQ is significant ( $\Delta ee = 2-10\%$  at RT versus 1-4% for DHQD derivatives). Especially noteworthy is the fact that the differences of selectivities obtained using 4a and 4b is very small for all examples in Table 12 and therefore enantiomers of the diol are available in almost the same optical purity.

The reaction can be successfully carried out at 0°C with a significant improvement of enantioselectivity especially for terminal olefins (entries 1,3 and 7).

In conclusion, we want to point out that from a large variety of olefinic substrates, it is now possible to obtain vicinal diols in excellent yields, with good to excellent enantiomeric enrichments for both diol enantiomers using either dihydroquinine or dihydroquinidine.

Example 23      Synthesis of Methylphenylcarbamoyl dihydroquinidine (MPC-DHQD):

Dihydroquinidine (1.4 g, 4.3 mmol, 1 eq) was dissolved in 15 ml of  $CH_2Cl_2$  under nitrogen atmosphere in a 3-necked 100 ml round bottom flask. At room temperature, 2 ml of triethylamine (14.4 mmol, 3.3 eq) was added to the solution and stirred for 30 minutes. N-methyl-N-phenylcarbamoyl chloride (1.6 g, 9.4 mmol, 2.2 eq) was dissolved in 6 ml  $CH_2Cl_2$  and added to the reaction mixture dropwise via an addition funnel. The reaction mixture was stirred under  $N_2$  for three days before reaching reaction completion. 50 ml of 2N NaOH were added, and the phases were separated. The  $CH_2Cl_2$

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layer was saved, and the aqueous phase was extracted with 50 ml of  $\text{CH}_2\text{Cl}_2$ . The  $\text{CH}_2\text{Cl}_2$  phases were combined and dried over  $\text{MgSO}_4$  before being concentrated down to afford a gummy pink material. Purification via flash

- 05 chromatography (silica gel, 95.5 EtOAc/ $\text{Et}_3\text{N}$ , v/v) afforded a yellow material which was then crystallized from  $\text{CH}_3\text{CN}$  to obtain white starlike crystals (1.27 g, 65% yield).

Characterization:

- 10 mp. 119-120° C. High resolution mass spec; calculated molecular mass-459.25217 amu, found-459.2519 amu.  
 $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$  with TMS); 8.7  $\delta$  (d, 1H), 8.0  $\delta$  (d, 1H), 7.2-7.4  $\delta$  (m, 7H) 6.4  $\delta$  (d, 1H), 3.8  $\delta$  (s, 3H), 3.3  $\delta$  (s, 3H), 3.1  $\delta$  (1H), 2.8  $\delta$  (q, 1H), 2.6  $\delta$  (m, 3H),  
15 1.7  $\delta$  (s, 2H), 1.3-1.4  $\delta$  (m, 7H), 0.9  $\delta$  (t, 3H).  
 $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$  with TMS): 12.1  $\delta$ , 23.9  $\delta$ , 25.3  $\delta$ , 26.2  $\delta$ , 27.3  $\delta$ , 37.5  $\delta$ , 38.2  $\delta$ , 49.8  $\delta$ , 50.7  $\delta$ , 55.5  $\delta$ , 59.7  $\delta$ , 75.6  $\delta$ , 75.6  $\delta$ , 101.8  $\delta$ , 119.1  $\delta$ , 121.8  $\delta$ , 126.3  $\delta$ , 126.7  $\delta$ , 127.3  $\delta$ , 129.1  $\delta$ , 131.7  $\delta$ , 143.1  $\delta$ ,  
20 144.7  $\delta$ , 144.9  $\delta$ , 147.5  $\delta$ , 152.1  $\delta$ , 154.8  $\delta$ , 157.7  $\delta$ .

Example 24      Asymmetric Dihydroxylation of Olefins  
Using 9-O-Carbamoyl Dihydroquinidine  
Ligands

- Typical Procedure for the Catalytic ADH (cis- $\beta$ -  
25 methylstyrene):

- To a well-stirred solution of DHQD-MPC (dihydroquinidine methylphenylcarbamate) (10 mg, 0.02 mmol, 0.10 equiv),  $\text{K}_3\text{Fe}(\text{CN})_6$  (200 mg, 0.6 mmol, 3 equiv),  $\text{K}_2\text{CO}_3$  (85 mg, 0.6 mmol, 3 equiv) in a tert-butanol/water solution (6 ml,  
30 1/1, v/v), osmium tetroxide was added in acetonitrile

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solution (0.5 M, 4  $\mu$ l, 0.01 equiv) at room temperature. After stirring for ten minutes, cis- $\beta$ -methylstyrene (26  $\mu$ l, 0.2 mmol) was added. The reaction mixture was stirred at room temperature, and reaction progress was  
05 monitored by thin layer chromatography. Upon reaction completion (less than two hours), the phases were separated. The aqueous phase was extracted with  $\text{CH}_2\text{Cl}_2$ . The tert-butanol and  $\text{CH}_2\text{Cl}_2$  fractions were combined and stirred for one hour with excess sodium metabisulfite and  
10 sodium sulfate. Concentration followed by flash chromatography afforded the diol (24.4 mg, 82% yield) as an off-white solid. Enantiomeric excess (ee) of the diol (46% ee) was determined by GC analysis of the bis-MPTA ester derivative.

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CLAIMS

1. A aromatic ether derivative of dihydroquinidine or dihydroquinine or salt thereof, wherein the aromatic ether is covalently attached to said dihydroquinidine or dihydroquinine at the asymmetric carbon.  
05
2. The aromatic ether derivative of dihydroquinidine or dihydroquinine of Claim 1 wherein said aromatic moiety is substituted and the substitution is a lower alkyl, alkoxy or halogen radical.
- 10 3. An aromatic ether derivative of quinidine or quinine or salt thereof wherein the aromatic ether is covalently attached to said quinidine or quinine at the asymmetric carbon.
- 15 4. The aromatic ether derivative of quinidine or quinine of Claim 3 wherein said aromatic moiety is substituted and wherein the substitution is a lower alkyl, alkoxy or halogen radical.
- 20 5. An aryl ether derivative of dihydroquinidine or dihydroquinine or salt thereof, wherein the aryl ether is covalently attached to said dihydroquinidine or dihydroquinine at the asymmetric carbon.

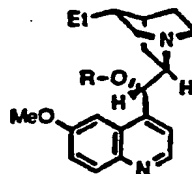
-93-

6. The aryl ether derivative of dihydroquinidine or dihydroquinine of Claim 5 wherein said aryl moiety is substituted and the substitution is a lower alkyl, alkoxy or halogen radical.
- 05 7. The aryl ether derivative of dihydroquinidine or dihydroquinine of Claim 5 wherein said aryl moiety is phenyl, substituted phenyl, a polycyclic benzenoid hydrocarbon or a substituted polycyclic benzenoid hydrocarbon.
- 10 8. A heterocyclic ether derivative of dihydroquinidine or dihydroquinine or salt thereof, wherein the heterocyclic ether is covalently attached to said dihydroquinidine or dihydroquinine at the asymmetric carbon.
- 15 9. The heterocyclic ether derivative of dihydroquinidine or dihydroquinine of Claim 8 wherein said heterocyclic moiety is substituted and the substitution is a lower alkyl, alkoxy or halogen radical.
- 20 10. The heterocyclic ether derivative of dihydroquinidine or dihydroquinine of Claim 9 wherein the heterocyclic moiety is a nitrogen heterocycle.

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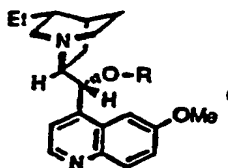
11. An ether which is a dihydroquinidine derivative or a dihydroquinine derivative wherein:

a) the dihydroquinidine derivative has the following formula:



05

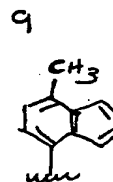
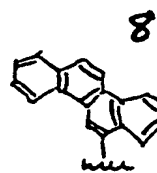
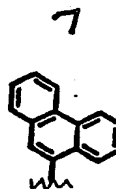
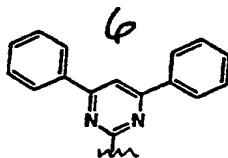
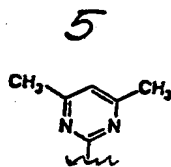
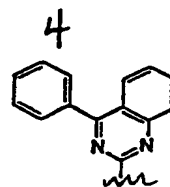
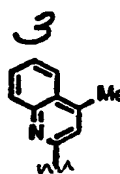
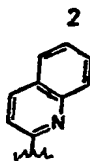
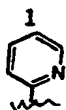
b) the dihydroquinine derivative has the following formula:



and;

c) R is:

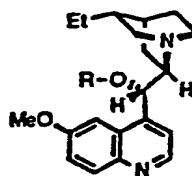
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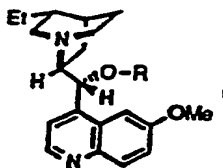
- 95 -

- 05
- 10) Phenyl
  - 11) Napthyl
  - 12) O-Methoxyphenyl
  - 13) Phenylcarbamoyl
  - 14) Methyl phenylcarbamoyl; or
  - 15) Diphenylcarbamoyl

12. A heterocyclic ether which is a dihydroquinidine derivative of the formula:

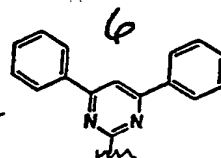
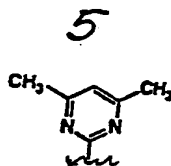
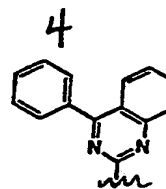
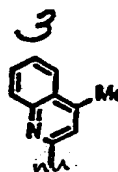
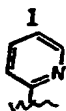


10 or a dihydroquinine derivative of the formula:



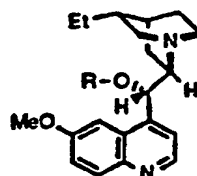
R is:

- and;

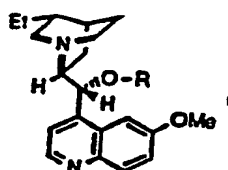


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13. An aryl ether which is a dihydroquinidine derivative of the formula:



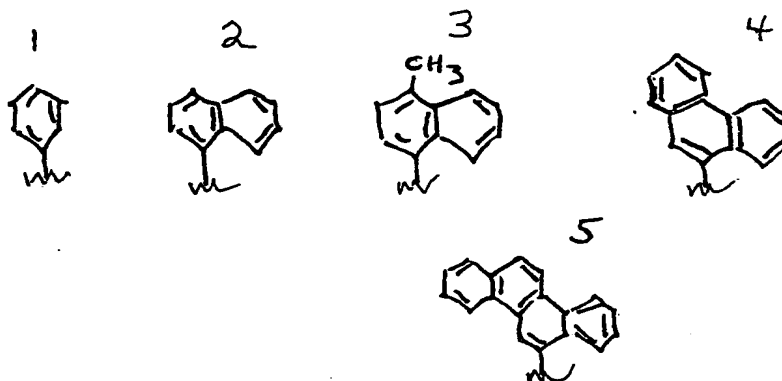
or a dihydroquinine derivative of the formula:



05

and;

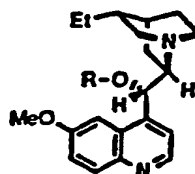
R is:



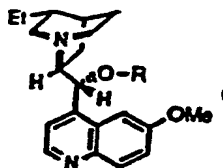
6) O-methoxyphenyl.

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14. A 9-O-carbamoyl which is a dihydroquinidine derivative of the formula:



or a dihydroquinine derivative of the formula:



and R is carbamate or an N substituted carbamate.

15. The 9-O-carbamoyl of Claim 14 wherein R is phenylcarbamoyl, methyl phenylcarbamoyl, or diphenylcarbamoyl.
- 10 16. An osmium-catalyzed method of producing an asymmetrically dihydroxylated olefin, comprising combining olefin; a chiral ligand which is an alkaloid or alkaloid derivative; an organic solvent; an aqueous solution; a base; an osmium-containing catalyst; and potassium ferricyanide, wherein the
- 15 alkaolid is an aromatic ether derivative of dihydroquinidine or an aromatic ether derivative of dihydroquinine and maintaining the resulting combination under conditions appropriate for
- 20 asymmetric addition to the olefin to occur.

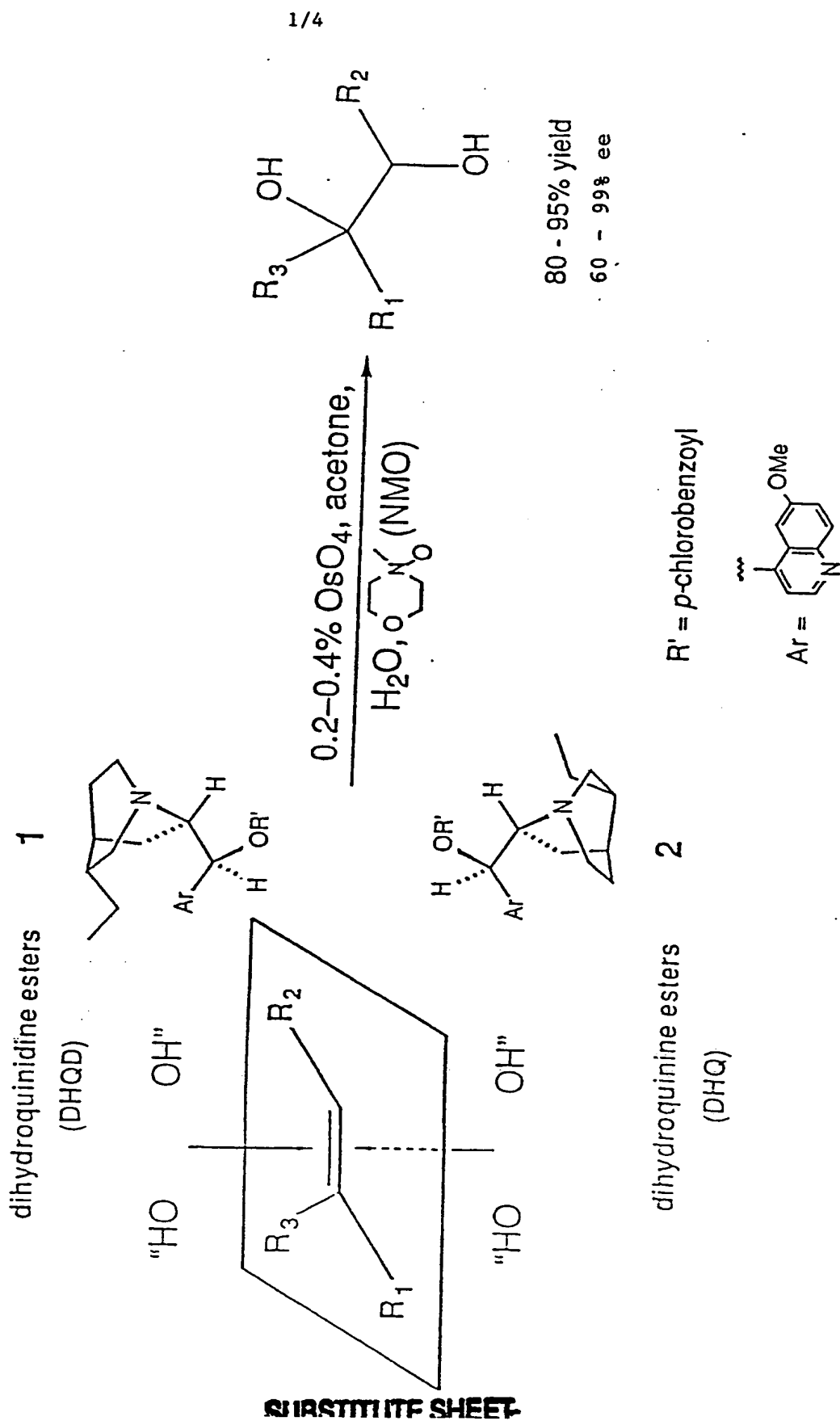
- 98 -

17. The method of Claim 16 wherein the chiral ligand is polymeric.
18. The method of Claim 16 wherein the aromatic ether is heterocyclic.
- 05 19. An osmium catalyzed method of producing an asymmetrically dihydroxylated olefin comprising:
- 10 a) combining an alkaloid or alkaloid derivative, an organic solvent, an aqueous solution, a base and potassium ferricyanide, wherein the alkaloid is an aromatic ether derivative of dihydroquinidine or an aromatic ether derivative of dihydroquinine;
- 15 b) adding an osmium-containing catalyst in a catalytic quantity to the reaction mixture; and
- c) adding the olefin to the combination formed in (b) and maintaining the resulting combination under conditions appropriate for asymmetric dihydroxylation of the olefin to occur.
- 20 20. The method of Claim 19 wherein the alkaloid or alkaloid derivative is polymeric.
21. The method of Claim 19 wherein the aryl ether is a heterocyclic.
22. The method of Claim 19 wherein the osmium catalyst is osmium tetroxide or potassium osmate (VI) dihydrate.
- 25

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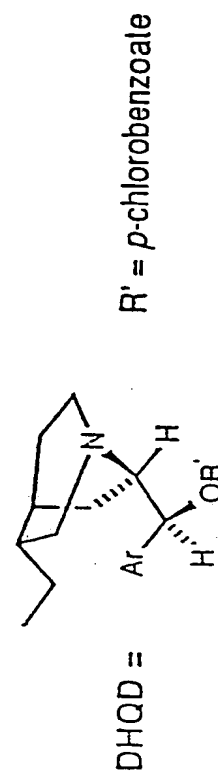
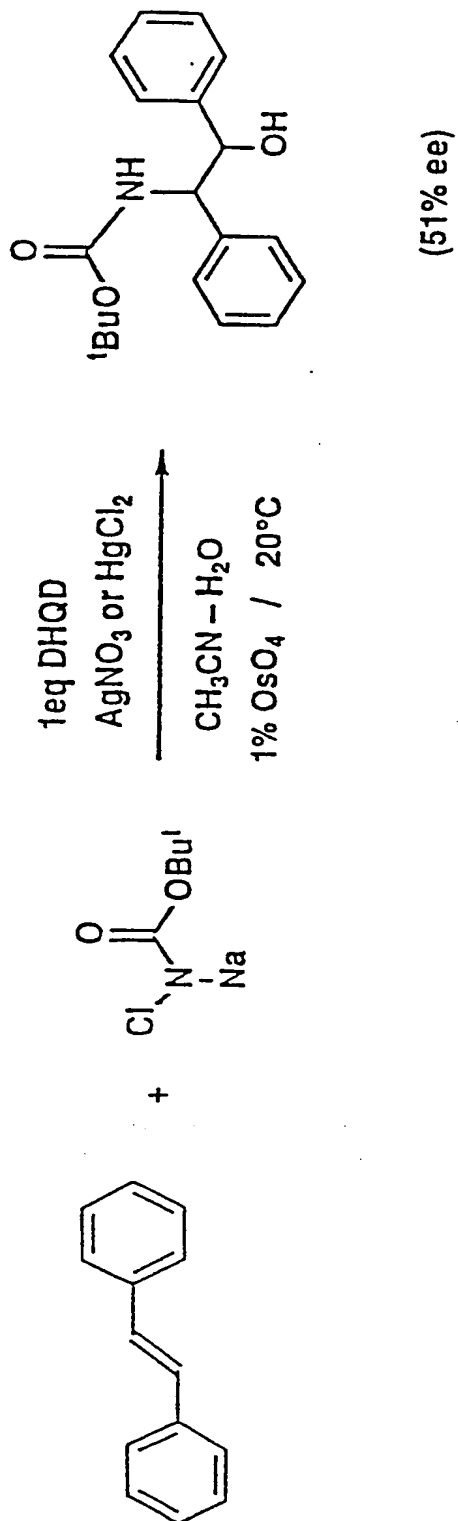
23. The method of Claim 19 wherein the organic solvent is cyclohexane, hexane, ethyl ether or t-butyl methyl ether.

**FIGURE 1**



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FIGURE 2  
Asymmetric Catalytic Oxyamination



SUBSTITUTE SHEET

FIGURE 3

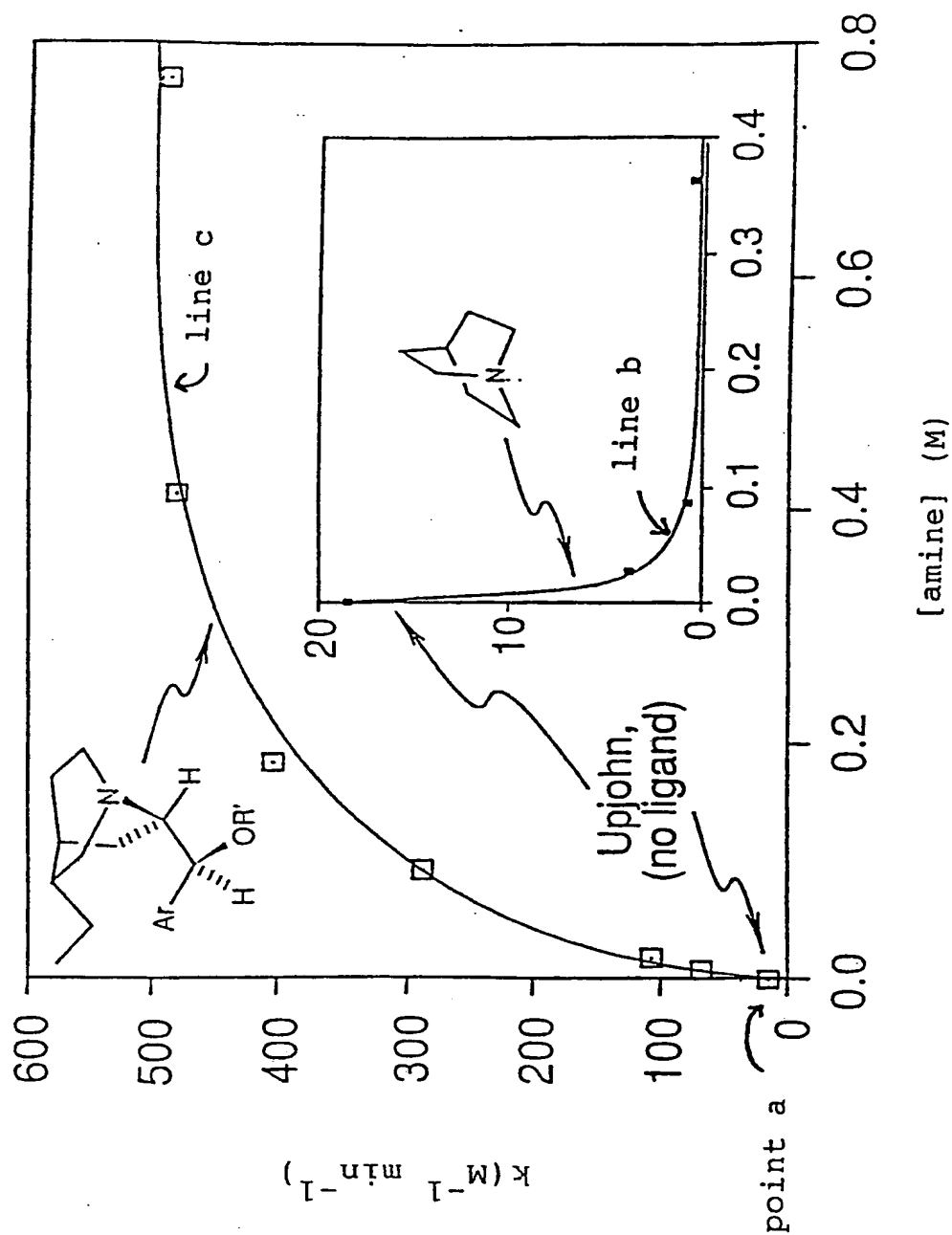
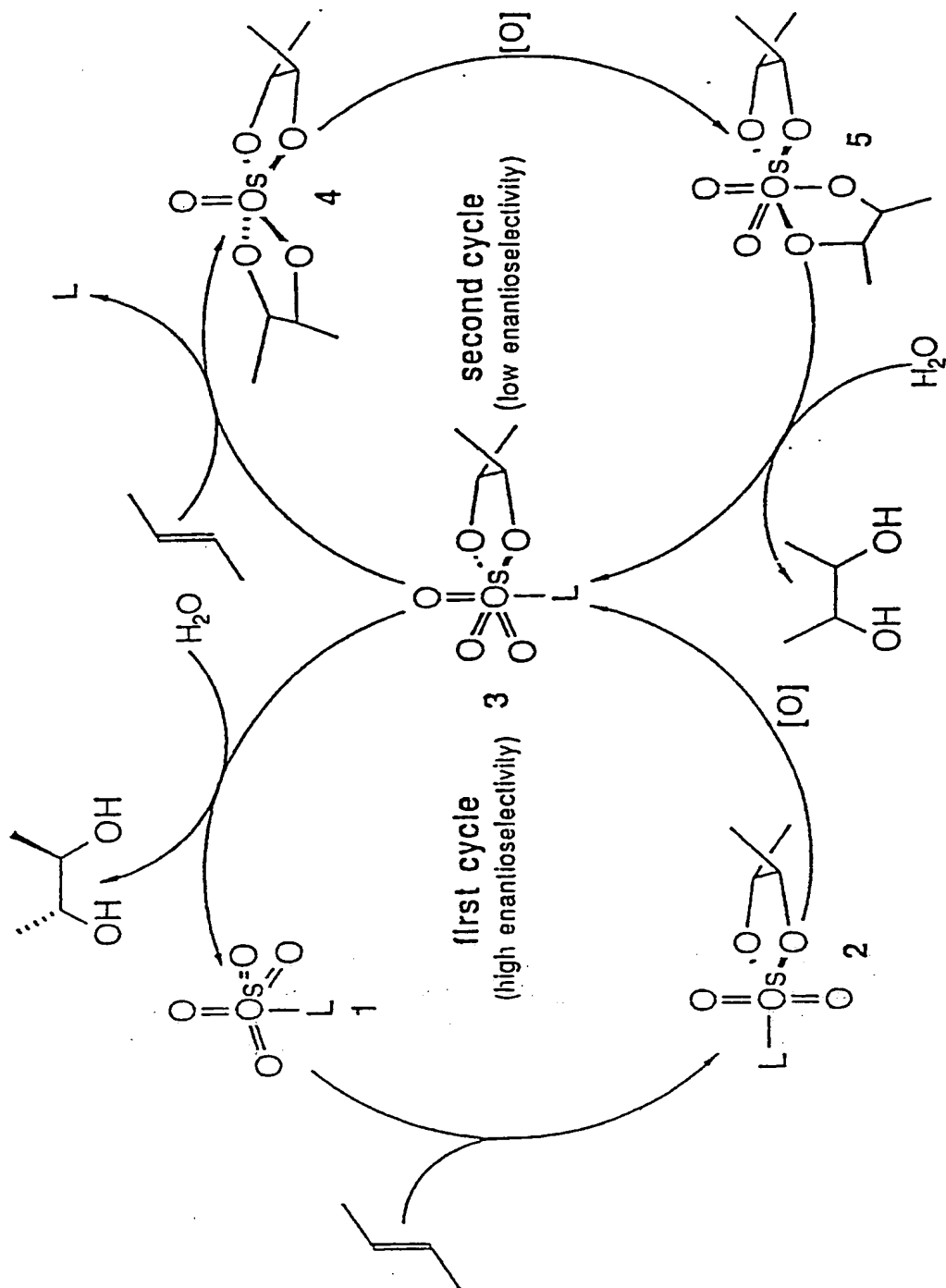


FIGURE 4



<b>I. CLASSIFICATION OF SUBJECT MATTER</b> (If several classification symbols apply, indicate all) <sup>6</sup> According to International Patent Classification (IPC) or to both National Classification and IPC Int.Cl. 5 C07D453/04											
<b>II. FIELDS SEARCHED</b> Minimum Documentation Searched? <table border="1"> <tr> <th>Classification System</th> <th>Classification Symbols</th> </tr> <tr> <td>Int.Cl. 5</td> <td>C07D</td> </tr> </table> Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched <sup>8</sup>			Classification System	Classification Symbols	Int.Cl. 5	C07D					
Classification System	Classification Symbols										
Int.Cl. 5	C07D										
<b>III. DOCUMENTS CONSIDERED TO BE RELEVANT<sup>9</sup></b> <table border="1"> <tr> <th>Category<sup>10</sup></th> <th>Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup></th> <th>Relevant to Claim No.<sup>13</sup></th> </tr> <tr> <td>X</td> <td>           TETRAHEDRON LETTERS.            vol. 31, no. 27, 1990, OXFORD GB            pages 3817 - 3820;            TOMOYUKI SHIBATA ET AL.: 'Ligand-based improvement of enantioselectivity in the catalytic asymmetric dihydroxylation of dialkyl substituted olefins.'            * complete document *         </td> <td>1-7, 11, 13, 16</td> </tr> <tr> <td>X</td> <td>           TETRAHEDRON LETTERS.            vol. 31, no. 21, 1990, OXFORD GB            pages 3003 - 3006;            B. MOON KIM ET AL.: 'Heterogeneous catalytic asymmetric dihydroxylation: use of a polymer-bound alkaloid.'            ---            ---            ---         </td> <td>1-7, 14, 16, 20</td> </tr> </table>			Category <sup>10</sup>	Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup>	Relevant to Claim No. <sup>13</sup>	X	TETRAHEDRON LETTERS. vol. 31, no. 27, 1990, OXFORD GB pages 3817 - 3820; TOMOYUKI SHIBATA ET AL.: 'Ligand-based improvement of enantioselectivity in the catalytic asymmetric dihydroxylation of dialkyl substituted olefins.' * complete document *	1-7, 11, 13, 16	X	TETRAHEDRON LETTERS. vol. 31, no. 21, 1990, OXFORD GB pages 3003 - 3006; B. MOON KIM ET AL.: 'Heterogeneous catalytic asymmetric dihydroxylation: use of a polymer-bound alkaloid.' --- --- ---	1-7, 14, 16, 20
Category <sup>10</sup>	Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup>	Relevant to Claim No. <sup>13</sup>									
X	TETRAHEDRON LETTERS. vol. 31, no. 27, 1990, OXFORD GB pages 3817 - 3820; TOMOYUKI SHIBATA ET AL.: 'Ligand-based improvement of enantioselectivity in the catalytic asymmetric dihydroxylation of dialkyl substituted olefins.' * complete document *	1-7, 11, 13, 16									
X	TETRAHEDRON LETTERS. vol. 31, no. 21, 1990, OXFORD GB pages 3003 - 3006; B. MOON KIM ET AL.: 'Heterogeneous catalytic asymmetric dihydroxylation: use of a polymer-bound alkaloid.' --- --- ---	1-7, 14, 16, 20									
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<b>IV. CERTIFICATION</b> <table border="1"> <tr> <td>           Date of the Actual Completion of the International Search            18 SEPTEMBER 1992         </td> <td>           Date of Mailing of this International Search Report            14. 10. 92         </td> </tr> <tr> <td>           International Searching Authority            EUROPEAN PATENT OFFICE         </td> <td>           Signature of Authorized Officer            VAN BIJLEN H.         </td> </tr> </table>			Date of the Actual Completion of the International Search 18 SEPTEMBER 1992	Date of Mailing of this International Search Report 14. 10. 92	International Searching Authority EUROPEAN PATENT OFFICE	Signature of Authorized Officer VAN BIJLEN H.					
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## III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X	TETRAHEDRON LETTERS. vol. 30, no. 16, 1989, OXFORD GB pages 2041 - 2044; B. BHUSHAN ET AL.: 'Documenting the scope of the catalytic asymmetric dihydroxylation.'	1-7, 16
A	WO,A,8 906 225 (MASSACHUSETTS INSTITUTE OF TECHNOLOGY) 13 July 1989 see claims	16, 19
A	TETRAHEDRON:ASYMMETRY vol. 1, no. 10, 1990, OXFORD GB pages 697 - 698; A.V. RAMA RAO ET AL.: 'Sharpless asymmetric dihydroxylation of aryloxy allyl ethers: a simple route to chiral beta-blockers.' * complete document *	16, 19
A	TETRAHEDRON LETTERS. vol. 31, no. 21, 1990, OXFORD GB pages 2999 - 3002; HOI-LUN KWONG ET AL.: 'Preclusion of the "second cycle" in the osmium-catalyzed asymmetric dihydroxylation of olefins leads to a superior process.'	16, 19
P,X	WO,A,9 116 322 (MASSACHUSETTS INSTITUTE OF TECHNOLOGY) 31 October 1991 * complete document *	1-13, 16-19
P,X	JOURNAL OF ORGANIC CHEMISTRY. vol. 56, no. 15, 19 July 1991, EASTON US pages 4585 - 4588; K.B. SHARPLESS ET AL.: 'New ligands double the scope of the catalytic asymmetric dihydroxylation of olefins.'	1-23
P,X	TETRAHEDRON LETTERS. vol. 32, no. 3819, 1991, OXFORD GB pages 5175 - 5178; D. PINI ET AL.: 'Heterogeneous catalytic asymmetric dihydroxylation of olefins with the OsO4/poly(9-O-acylquinine-co-acrylonitrile) system.'	1-7, 13, 16, 17, 19, 20
P,X	TETRAHEDRON LETTERS. vol. 33, no. 1614, 14 April 1992, OXFORD GB pages 2095 - 2098; RYU OI ET AL.: 'Asymmetric dihydroxylation of acrolein acetals: synthesis of stable equivalents of enantiopure glyceraldehyde and glycidialdehyde.'	1-7, 13, 16

## III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
P, X	<p>TETRAHEDRON LETTERS. vol. 32, no. 41, 1991, OXFORD GB pages 5761 - 5764; YASUKAZU OGINO ET AL.: 'A ligand structure-enantioselectivity relationship for the osmium-catalyzed asymmetric dihydroxylation of olefins.' * complete document *</p> <p>---</p>	1-13, 16

**ANNEX TO THE INTERNATIONAL SEARCH REPORT  
ON INTERNATIONAL PATENT APPLICATION NO.**

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SA 60572

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-8906225	13-07-89	US-A- 4871855	03-10-89
		US-A- 4965364	23-10-90
		EP-A- 0395729	07-11-90
		JP-T- 3503885	29-08-91
		US-A- 5126494	30-06-92
WO-A-9116322	31-10-91	US-A- 5126494	30-06-92

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